EPA Registration # 86833-1

Volume 1

Part 2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

January 17, 2017

Kathleen M. Sanzo
Counsel for Humane Society of the U.S.
Morgan, Lewis & Bockius
1111 Pennsylvania Avenue, N.W.
Washington, DC 20004

Subject: Label Amendment – Adding deer & other members of the family Cervidae to current label
Product Name: ZonaStat H
EPA Registration Number: 86833-1
Application Date: 12/24/2015
Decision Number: 520669

Dear Ms. Sanzo:

The amended label referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide and Rodenticide Act, as amended, is not acceptable for the following reasons:

1. The Storage Stability and Corrosion Characteristics data which was a condition of registration has not been submitted for review.
2. The label changes that were a condition of registration have not been made to the master label.
3. The label changes requested by the Agency on 8/3/16 have not been made to the master label. The label changes are attached here for your convenience.

Therefore, your application is not acceptable. No further processing of this application will occur. If you have any questions, please contact Marianne Lewis by phone at (703) 308-8943, or via email at lewis.marianne@epa.gov.

Sincerely,

Mark Suarez
Product Manager 07
Invertebrate & Vertebrate Branch 3
Registration Division (7505P)
Office of Pesticide Programs

Dear Ms. Sanzo:

In order to move forward with the label amendment for your product, EPA Reg. No. 86833-1, please revise your label as follows:

RESTRICTED USE PESTICIDE

For retail sale to and use only by Certified Applicators or persons under their direct supervision of the following organizations and their designated wildlife management personnel and only for those uses covered by the Certified Applicator's certification:

- Department of Interior and all its designated agents
- National Park Service, US Fish & Wildlife Service, Bureau of Land Management
- USDA and all its designated agents (i.e., U.S. Forest Service, Animal and Plant Health Inspection Service)
- State Agencies for agriculture/livestock & wildlife
- Federally recognized Indian Tribes
- Department of Defense
- Humane Society of the United States

Each Responsible Authority must sign a certification of use prior to the administration of the vaccine to any animals. The certification statement is attached to this label.

Sublabel A

ZONASTAT-H

Zonastat-H is a porcine zona pellucida immunocontraceptive vaccine indicated for use in limiting the populations of wild and feral horses (Equus caballus) and burros (Equus asinus).

Active Ingredients:

Porcine zona pellucida (ZP3)(0.1%)	0.071%
Porcine zona pelluciad (ZP1, ZP2, ZP4)(0.1%)	0.029%
Other Ingredients:	99.900%
Total	100.000%

This product contains 100 µg of PZP per 0.04 oz (0.5 mL)

EPA Reg. No. 86833-x
EPA Est. No. 090192-MT-001

Net Contents: 0.5 mL

Humane Society of the United States
700 Professional Drive
Gaithersburg, MD 20879

Expiration date: (since the frozen PZP antigen expires after 2 years – label needs to have an expiration date on it.)

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
IF ON SKIN OR CLOTHING	Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice. Needle stick or cut: clean wound immediately with soapy water and disinfect the wound with alcohol or other bactericidal solution. Contact with Freund's Complete Adjuvant: wipe skin clean with an ethanol soaked towelettes and wash with soapy water
IF INHALED	Move person to fresh air. If person is not breathing, call 911 or ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for treatment advice.
IF IN EYES	Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.
Have the product container or label with you when calling a poison control center or doctor or going for treatment. Accidental injection may cause infertility in women.	

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Harmful if absorbed through skin. Harmful if inhaled. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Avoid breathing spray mist.

Personal Protective Equipment (PPE)

Mixers, loaders and applicators must wear:

- Long sleeved shirt and long pants
- Shoes
- Socks

- Chemical resistant gloves made out of: barrier laminate, butyl rubber ≥14 mils, nitrile rubber≥14 mils, neoprene rubber ≥14 mils, natural rubber ≥14 mils, polyethylene, polyvinyl chloride ≥14 mils, or viton ≥14 mils

Environmental Hazards

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment rinse waters or rinsate.

DIRECTIONS FOR USE

Restricted Use Pesticide

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

Read this entire label and follow all use directions and precautions.

Restrictions

- Only for use on female wild and feral horses and burros
- All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery.
- Do not expose children, pets, or other non-target animals to this product.
- Do not apply this product to food or feed.
- Do not apply this product to horses or burros being used as food.
- This product is only for use on female wild and feral horses and burros, which are defined as free-roaming horses or burros, privately or publicly owned, that are capable of doing environmental damage.

Product Information

When injected into a female wild and feral horse or burro, ZonaStat-D stimulates the production of anti-zona pellucida (ZP) antibodies. These antibodies bind to the native ZP glycoproteins surrounding the egg of the target female, alter their conformation, and block sperm attachment preventing conception.

Equipment Needed:

<u>For Mixing</u>
glass syringes, 5.0 cc, graduated at 0.2 cc, with Luer-Loc
1.5 inch 18 g disposable sterile needle

Freund's Adjuvant
PZP Solution (PZP antigen dissolved in phosphate buffered saline solution)
Luer-Loc connector

For Hand Delivery
3 cc disposable plastic syringe w/Luer-Loc
1.5 inch 18 g disposable sterile needle

For Jab-Stick Delivery
Jab Stick
3 cc disposable plastic syringe with Luer-Loc
1.5 inch 14 g disposable sterile needle

For Remote Dart Delivery
2.0 inch 18 g disposable sterile needle
1.0 cc dart with 1.25 inch or 1.5 inch barbless needle

Application Rate:

For maximum efficacy, ZonaStat-H is administered as an initial priming dose followed by a booster dose at least two weeks later. Efficacy is maintained by annual booster doses.

Initial Priming Dose: Is 0.5 cc of the PZP Solution emulsified with 0.5 cc modified Freund's Complete Adjuvant. If followed by a booster dose, the priming dose may be administered at any time of the year. The priming dose alone is expected to reduce pregnancy rates by 55-70% for one year if administered one to three months prior to the onset of mating season.

Booster Dose: Is 0.5 cc of the PZP Solution emulsified in 0.5 cc modified Freund's Incomplete Adjuvant (which adjuvant?). Administration of a single booster treatment at least 2 weeks after the administration of the priming dose is expected to reduce pregnancy rates by 90-95% for one year. Efficacy in subsequent years is maintained by administering an annual booster dose.

Procedures:

Mixing

1. Gloves must be worn at all times
2. Attach the Luer-Lok connector to one of the glass syringes
3. Attach the 1.5 inch needle on the second glass syringe
4. Draw out 0.5 cc of adjuvant
5. Using the same syringe, draw up the 0.5 cc of PZP in phosphate buffered saline solution

6. Holding the syringe containing the vaccine very care (to prevent the plunger from slipping out), take off the needle and attach the syringe to the second syringe using the Luer-Lok connector.
7. Push the PZP solution-adjuvant mixture back and forth through the two syringes 100 times. The resulting emulsion will become thick and look white. THIS PROCEDURE IS VERY IMPORTANT AND IS RELATED TO THE PRESENTATION OF THE ANTIGEN AND THE SUBSEQUENT EFFICACY OF THE PRODUCT.
8. Make sure that all of the emulsion is in one syringe.
9. Holding the syringe containing the emulsion very carefully, remove the other syringe, leaving the Luer-Lok on the syringe containing the emulsion.

Application:
For Hand Delivery Injection, attach a 2.0 or 3.0 cc plastic syringe to the glass syringe via the Luer-Lok, and inject the emulsion into the plastic syringe. After loading the plastic syringe, disconnect the glass syringe and connect an 18 g 1.5 inch needle to the plastic syringe containing the emulsion.

For Jab Stick Delivery, place the nose of the plastic syringe tightly into the Luer-Lok and inject the emulsion from the glass syringe into the plastic syringe. After filling the plastic syringe, remove the glass syringe and attach the 14 g 1.5 inch needle to the plastic syringe containing the emulsion. Place the plastic syringe into the jab stick.

For Remote Dart Delivery, attach the 18 g 2 inch needle to the glass syringe containing the emulsion. Insert the needle into the body of the dart through the dart needle, and inject the contents of the syringe into the dart. Apply a small amount of Vaseline to the dart tip.

After the antigen solution and adjuvant are emulsified in the field and loaded into the dart, remotely inject ZonaStat-H intramuscularly in the hip or gluteus or hamstring muscles using a syringe dart fired from a CO_2 or cartridge-powered projection system.

Use the Pneu-Dart 1.0 cc dart with a 1.25 inch or 1.5 inch barbless needle for delivery.

The darts can be delivered using any of the following rifles, depending on the logistical requirements of the particular targeted population:

- Dan-Inject CO_2 rifle (Wildlife Pharmaceuticals) with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)
- Dan-Inject Pistol Grip Blow Gun with a 13 mm barrel (for use at ranges of 5 meters to 20 meters)
- Pneu-Dart model 193 rifle (for use at ranges of up to 50 meters)
- Pneu-Dart model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)
  Make sure that these models are still being marketed

All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its contents.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal

Pesticide Storage: The frozen PZP antigen expires after two years. Keep vials of PZP antigen frozen until ready for use. When transporting for use in the field, keep PZP antigen stored in a cooler, with ice packs. Once defrosted the PZP antigen expires after 24 hours. If transportation takes longer than 8 hours, store PZP antigen on dry ice in the cooler. Keep adjuvant refrigerated at +2° C to +8° C, but not frozen, until ready to be mixed with the PZP antigen. Store loaded darts in a cool dry area.

Pesticide Disposal: For any unused product dispose of as medical waste according to Federal, State, and Local regulations.

Container Disposal: Non-refillable container. Do not reuse or refill container. Dispose of expired material, preloaded syringes, used syringes as medical waste according to applicable Federal, State, and Local regulations. All used darts and needles are to be placed in a Sharps container and disposed of as medical waste according to applicable Federal, State and Local regulations.

RESTRICTED USE PESTICIDE

For retail sale to and use only by Certified Applicators or persons under their direct supervision of the following organizations and their designated wildlife management personnel and only for those uses covered by the Certified Applicator's certification:

- Department of Interior and all its designated agents
- National Park Service, US Fish & Wildlife Service, Bureau of Land Management
- USDA and all its designated agents (i.e., U.S. Forest Service, Animal and Plant Health Inspection Service)
- State Agencies for agriculture/livestock & wildlife
- Federally recognized Indian Tribes
- Department of Defense
- Humane Society of the United States

Each Responsible Authority deer intended to be treated with Zonastat-D must sign a certification of use prior to the administration of the vaccine to any animals. The certification statement is attached to this label.

Sublabel B

ZONASTAT-D

Zonastat-D is a porcine zona pellucida immunocontraceptive vaccine indicated for use in limiting the populations of white tailed deer (Odocoileus virginianus) and other members of the family Cervidae.

Active Ingredients:

Porcine zona pellucida (ZP3)(0.1%)	0.071%
Porcine zona pelluciad (ZP1, ZP2, ZP4)(0.1%)	0.029%
Other Ingredients:	99.900%
Total	100.000%

This product contains 100 µg of PZP per 0.04 oz (0.5 mL)

EPA Reg. No. 86833-x
EPA Est. No. 090192-MT-001

Net Contents: 0.5 mL

Humane Society of the United States
700 Professional Drive
Gaithersburg, MD 20879

Expiration date: (since the frozen PZP antigen expires after 2 years – label needs to have an expiration date on it.)

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
IF ON SKIN OR CLOTHING	Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice. Needle stick or cut: clean wound immediately with soapy water and disinfect the wound with alcohol or other bactericidal solution. Contact with Freund's Complete Adjuvant: wipe skin clean with an ethanol soaked towelettes and wash with soapy water
IF INHALED	Move person to fresh air. If person is not breathing, call 911 or ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for treatment advice.
IF IN EYES	Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.
Have the product container or label with you when calling a poison control center or doctor or going for treatment. Accidental injection may cause infertility in women.	

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Harmful if absorbed through skin. Harmful if inhaled. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Avoid breathing spray mist.

Personal Protective Equipment (PPE)

Mixers, loaders and applicators must wear:

- Long sleeved shirt and long pants
- Shoes
- Socks
- Chemical resistant gloves made out of: barrier laminate, butyl rubber ≥14 mils, nitrile rubber≥14 mils, neoprene rubber ≥14 mils, natural rubber ≥14 mils, polyethylene, polyvinyl chloride ≥14 mils, or viton ≥14 mils

Environmental Hazards

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment rinse waters or rinsate.

DIRECTIONS FOR USE

Restricted Use Pesticide

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

Read this entire label and follow all use directions and precautions.

Restrictions

- Only for use on female deer
- All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery.
- Do not expose children, pets, or other non-target animals to this product.
- Do not apply this product to food or feed.
- Do not apply this product to deer being used as food.
- This product is only for use on female deer, which are defined as free-roaming deer, privately or publicly owned, that are capable of doing environmental damage.

Product Information

When injected into a female deer, ZonaStat-D stimulates the production of anti-zona pellucida (ZP) antibodies. These antibodies bind to the native ZP glycoproteins surrounding the egg of the target female, alter their conformation, and block sperm attachment.

Equipment Needed:

For Mixing
glass syringes, 5.0 cc, graduated at 0.2 cc, with Luer-Loc
1.5 inch 18 g disposable sterile needle (thought you needed smaller needle?)
Freund's Adjuvant
PZP Solution (PZP antigen dissolved in phosphate buffered saline solution)
Luer-Loc connector

For Remote Dart Delivery
2.0 inch 18 g disposable sterile needle

1.0 cc dart with 1.25 inch or 1.5 inch barbless needle

Application Rate:

For maximum efficacy, ZonaStat-D is administered as an initial priming dose followed by a booster dose at least two weeks later. Efficacy is maintained by annual booster doses.

Initial Priming Dose: Is 1.0 cc of the PZP Solution/modified Freund's Complete Adjuvant emulsion. If followed by a booster dose, the priming dose may be administered at any time of the year. The priming dose alone is expected to reduce pregnancy rates by 55-70% for one year if administered one to three months prior to the onset of mating season. (please revise this if needed to work for deer)

Booster Dose: Is 0.5 cc of the PZP Solution emulsified in 0.5 cc modified Freund's Incomplete Adjuvant (which adjuvant?). Administration of a single booster treatment at least 2 weeks after the administration of the priming dose is expected to reduce pregnancy rates by 90-95% for one year. Efficacy in subsequent years is maintained by administering an annual booster dose. (please revise this if needed to work for deer)

Procedures:

Mixing

1. Gloves must be worn at all times
2. Attach the Luer-Lok connector to one of the glass syringes
3. Attach the 1.5 inch needle on the second glass syringe
4. Draw out 0.5 cc of adjuvant
5. Using the same syringe, draw up the 0.5 cc of PZP in phosphate buffered saline solution
6. Holding the syringe containing the vaccine very care (to prevent the plunger from slipping out), take off the needle and attach the syringe to the second syringe using the Luer-Lok connector.
7. Push the PZP solution-adjuvant mixture back and forth through the two syringes 100 times. The resulting emulsion will become thick and look white. THIS PROCEDURE IS VERY IMPORTANT AND IS RELATED TO THE PRESENTATION OF THE ANTIGEN AND THE SUBSEQUENT EFFICACY OF THE PRODUCT.
8. Make sure that all of the emulsion is in one syringe.
9. Holding the syringe containing the emulsion very carefully, remove the other syringe, leaving the Luer-Lok on the syringe containing the emulsion.

Application:

For Remote Dart Delivery, attach the 18 g 2 inch needle to the glass syringe containing the emulsion. Insert the needle into the body of the dart through the dart needle, and inject the contents of the syringe into the dart. Apply a small amount of Vaseline to the dart tip.

After the antigen solution and adjuvant are emulsified in the field and loaded into the dart, remotely inject ZonaStat-H intramuscularly in the hip or gluteus or hamstring muscles using a syringe dart fired from a CO_2 or cartridge-powered projection system.

Use the Pneu-Dart 1.0 cc dart with a 1.25 inch or 1.5 inch barbless needle for delivery.

The darts can be delivered using any of the following rifles, depending on the logistical requirements of the particular targeted population:

- Dan-Inject CO_2 rifle (Wildlife Pharmaceuticals) with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)
- Dan-Inject Pistol Grip Blow Gun with a 13 mm barrel (for use at ranges of 5 meters to 20 meters)
- Pneu-Dart model 193 rifle (for use at ranges of up to 50 meters)
- Pneu-Dart model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)
  Make sure that these models are still being marketed

All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its contents.

STORAGE AND DISPOSAL
Do not contaminate water, food or feed by storage or disposal

Pesticide Storage: The frozen PZP antigen expires after two years. Keep vials of PZP antigen frozen until ready for use. When transporting for use in the field, keep PZP antigen stored in a cooler, with ice packs. Once defrosted the PZP antigen expires after 24 hours. If transportation takes longer than 8 hours, store PZP antigen on dry ice in the cooler. Keep adjuvant refrigerated at +2° C to +8° C, but not frozen, until ready to be mixed with the PZP antigen. Store loaded darts in a cool dry area.

Pesticide Disposal: For any unused product dispose of as medical waste according to Federal, State, and Local regulations.

Container Disposal: Non-refillable container. Do not reuse or refill container. Dispose of expired material, preloaded syringes, used syringes as medical waste according to applicable Federal, State, and Local regulations. All used darts and needles are to be placed in a Sharps container and disposed of as medical waste according to applicable Federal, State and Local regulations.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

December 15, 2016

Michael Harris
Legal Director, Wildlife Law Program
Friends of Animals
Western Region Office
7500 E. Arapahoe Rd, Suite 385
Centennial, CO 80112

Subject: Petition to Conduct a Special Review of Contraceptive ZonaStat-H, EPA Reg. No. 86833-1

Dear Mr. Harris:

This letter is a response to your petition on behalf of Friends of Animals (FoA) to Administrator McCarthy dated May 19, 2015, related to a pesticide registration for ZonaStat-H, EPA Reg. No. 86833-1 issued by the Environmental Protection Agency (EPA) on January 30, 2012. ZonaStat-H contains the active ingredient porcine zona pellucida (PZP), which elicits the creation of antibodies in the target animal that surround the egg and block the attachment of sperm, preventing fertilization.

In your petition and its cover letter, you specifically requested the EPA: 1) pursuant to 40 CFR §154.1 *et seq*. to conduct a Special Review to consider scientific evidence demonstrating the need to cancel or reclassify this registration; 2) pursuant to section 6(c)(1) of the Federal Insecticide Fungicide and Rodenticide Act (FIFRA), 7 USC § 136d(c)(1) to issue an order to suspend this registration during the special review and/or proceeding to cancel or reclassify; or 3) pursuant to section 6(b)(2) of FIFRA, 7 USC § 136d(b)(2) to hold a hearing to determine if this registration should be canceled or reclassified. You supported these requests with information alleging that, because of its effectiveness as a contraceptive, ZonaStat-H adversely affects wild horses by changing their social behavior and causing physiological effects such as prolonged infertility or foals born out of the regular birthing season.

ZonaStat-H is a pesticide, as defined in section 2(u) of FIFRA, because it is intended to "prevent, destroy, repel, or mitigate a pest," which is defined, in part, at 40 CFR 152.5 as "any vertebrate animal other than man" "under circumstances that make it deleterious to man or the environment." In some circumstances, wild horses and burros may be pests. Without population control, herds may reach levels that surpass what the land can support. These herds over-graze the landscape, damage habitats, outcompete native species such as bighorn sheep, and in some cases invade residential areas. Specifically, ZonaStat-H's label limits its use to female wild and feral horses or burros that are capable of doing environmental damage.

When EPA registered ZonaStat-H, EPA considered the toxicity of the active ingredient and its potential risks of toxic effects. EPA waived requirements for toxicity studies "due to the lack of toxicity in the target animal; a history of safe use of the vaccine…; the mode of action and fate of the product's metabolites; the limited opportunity of exposure to non-target animals, applicators, and the public; and lack of immunotoxicity as shown in the published scientific literature."[1] For most pesticides, EPA is not concerned with toxic effects on target pests. Here, however, where the pesticidal intent is only to control reproduction, EPA considered information about the mode of action and fate of the product's metabolites and found the product was not likely to be toxic or pathogenic to either the target animals or nontarget organisms. EPA also waived required studies for ecological effects and environment fate due to the limited exposure to non-target organisms and limited concern for secondary exposure to carnivores.[2] Your petition does not contest any of these findings. Rather, your concerns revolve around the choice to use ZonaStat-H as a population management tool.

As stated in your petition, the Wild Horses and Burros Act (WHBA) mandates that the Bureau of Land Management (BLM) and US Forest Service (USFS) "manage wild free-roaming horses and burros in a manner that is designed to achieve and maintain a thriving natural ecological balance on the public lands." 16 USC § 1333(a). Further, section 1333(b) of the WHBA mandates BLM maintain an inventory of wild horses to "determine whether appropriate management levels should be achieved by the removal or destruction of excess animals, or other options (such as sterilization, or natural controls on population levels.)" 16 USC § 1333(b).

In light of the fact that wild horse management experts who use ZonaStat-H have far greater expertise than EPA in managing wild horse populations as well as the legal responsibility for appropriately managing them, EPA has determined the appropriateness of the use of the contraceptive when considering potential adverse effects on the wild horse herds themselves is best left to horse management experts in determining where, when, and whether to use the pesticide. Those experts are in the best position to decide if contraception, with whatever effects may accompany it, is the appropriate method of management over other management tools such as removal of individual horses.

While Special Review can be conducted at the request of a petitioner or on the initiative of EPA, whether to conduct a Special Review is at the Agency's discretion ("The Administrator may conduct a Special Review if …" 40 CFR 154.7(a)). As noted in 40 CRF 154.5, EPA is guided in its decisions regarding Special Review by the principle that the burden of persuasion that a pesticide product is entitled to continued registration is on the proponent of registration. However, EPA does not consider this principle to limit its discretion in determining whether a Special Review is an appropriate activity for the Agency to undertake. Thus, while FoA suggests it has made a *prima facie* case for initiating Special Review, providing some evidence and argument for initiating Special Review does not compel EPA to do so.

The criteria for initiating Special Review are set out in 40 CFR 154.7. The petition argues that Special Review should be based upon the contentions that 1) PZP can result in residues in the

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[1] Registration of Contraceptive ZonaStat-H, for Population Control of Wild and Feral Horses and Burros (2/9/2012) at 3.
[2] Id at 5.

environment of nontarget organisms that equal or exceed concentrations that are toxic to those organisms; 2) PZP may otherwise pose a previously undisclosed risk to the environment which is of sufficient magnitude to merit Special Review; and 3) the use of PZP violates the Wild Horses and Burros Act. Each will be addressed below:

1) PZP can result in residues in the environment of nontarget organisms – the foals of treated mares conceived and birthed post application -- that equal or exceed concentrations that are toxic to those organisms

The petitioners argue that treatment with PZP will: increase reproductive behaviors at suboptimal times; increase the likelihood that birth will also occur at suboptimal times; and increase the likelihood of foal mortality.

EPA Response:

Petitioners are attempting to fit the effects related to the effectiveness of ZonaStat-H within listed regulatory criteria that may trigger Special Review, specifically here, 40 CFR 154.7(a)(3). However, this criterion is intended to address the harmful effects of pesticides on nontarget organisms that are unintentionally exposed to a pesticide in the environment. The target organisms for PZP are the female horses or burros that have the potential to cause harm (as defined above). Any effects to foals are due to PZP being effective to various degrees in the target mare. Peer-reviewed research has shown that female foals born to PZP-treated mares are fertile and that there is no long-term effect to the fertility of foals. As stated above, EPA believes the decision on whether ZonaStat-H is the appropriate population control tool to use in a given situation is best made by the wild horse management experts such as BLM or USFS, to whom Congress has given the responsibility to manage wild horse herds in the United States, or by the management experts working for the various other EPA-approved users, including the Department of Defense, Indian tribes, and public and private wild horse sanctuaries.

2) PZP may otherwise pose a previously undisclosed risk to the environment which is of sufficient magnitude to merit a Special Review:

The petition cites articles and research believed to demonstrate changes in mare stress and reproductive physiology along with changes in herd behavior. Specifically, the petition contends that: recent research suggests ZonaStat-H poses risk of immediate physical damage to the dosed mare; for foals born to previously treated mares there may be increased foal mortality; use of ZonaStat-H may cause social disruptions among herds w/treated mares; and this changed behavior places the herd at risk for genetic bottleneck.[3]

EPA Response:

The administration of ZonaStat-H does not produce immediate physical damage to the dosed mare. This immunocontraceptive is highly target specific, the egg's zona pellucida, with few

[3]A genetic or population bottleneck is defined as a large reduction in population size, resulting in less genetic diversity, over one or more generations.

physical side effects other than minor injection site issues. Repeated use may, in some cases, cause prolonged infertility, which is consistent with the pesticidal goal of reduced fertility. No demonstrated changes to other organ systems have been documented. Mares that have been treated with ZonaStat-H appear to be in better overall body condition since they do not have to go through the high energetic demands of pregnancy and lactation and most appear to live longer.

Reducing the number of fertile mares by the administration of immunocontraceptives could have an effect on the genetic diversity of the herd. But this is fundamentally a question of how the herds of wild horses should be managed. The rounding up of mares and permanently removing them from their herds would also have effects on the genetic diversity of the herd. Again, EPA believes this issue is best decided by the experts selected by Congress to manage wild horse populations in the United States.

3) The use of PZP violates the WHBA

EPA Response:

As discussed above, the WHBA is administered by BLM and USFS and, as such, EPA will not make any determinations on whether the use of PZP is a violation of the WHBA. That is an issue EPA believes must be left to BLM and USFS to resolve. ZonaStat-H is also approved for use by other entities including agencies and Indian tribes that manage feral horses and burros that are not subject to regulation under the WHBA. Nevertheless, even if use of PZP was a violation of the WHBA, a violation of another law is not a basis for which to initiate a Special Review.

Conclusion

Having considered the information provided in your petition, EPA has concluded that initiating a Special Review is not warranted at this time. The fundamental issues your petition raised concern whether choosing to use PZP is an appropriate method to manage wild horse populations. EPA has concluded that is best determined by horse management experts who can determine what is appropriate based on a specific factual scenario. To the extent petitioners want wild horse herds managed differently, they must take their arguments to those charged with managing the wild horse herds rather than to EPA.

In addition to the arguments laid out in your petition, the cover letter to the petition requested EPA issue an order to suspend this registration during the special review and/or proceeding to cancel or reclassify; or hold a hearing, pursuant FIFRA 6(b)(2) to determine if this registration should be canceled or reclassified. The petition did not provide information suggesting PZP presents an imminent hazard as defined in section 2(l) of FIFRA. To issue a suspension order, EPA must determine that such an order is necessary to prevent an imminent hazard and the suspension order must be issued concurrently with a notice of intent to cancel or reclassify a pesticide. (See FIFRA § 6(c)(1).) EPA has not made such a determination, nor will it be issuing a notice of intent to cancel or reclassify. Therefore EPA cannot suspend the registration. Finally, consistent with the discussion above, EPA declines to exercise its discretion to hold a hearing

pursuant to section 6(b)(2) of FIFRA to determine whether or not this registration should be cancelled or its classification changed.

For the reasons discussed in this document, the petition is Denied.

Sincerely,

Jack E. Housenger, Director

Office of Pesticide Programs

Morgan Lewis

Kathleen M. Sanzo
Partner
+1.202.739.5209
kathleen.sanzo@morganlewis.com

October 25, 2016

VIA Email and U.S. Mail

Marianne Lewis
Biologist
IVB3 / RD
Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202-3553

Dear Ms. Lewis:

Please find attached the revised label for the ZonaStat-D product, plus HSUS comments on various questions you raised in your last submission to us, dated August 3, 2016.

Please let us know if you have any questions on the attached.

Sincerely,

Kathleen M. Sanzo
Counsel for The Humane Society of the United States

Attachment

Morgan, Lewis & Bockius LLP

1111 Pennsylvania Avenue, NW
Washington, DC 20004
United States

T +1.202.739.3000
F +1.202.739.3001

ONLY ADDRESSED THIS PORTION - DIDN'T MAKE CHANGES TO SUBLABEL A ? DON'T KNOW THEY DIDN'T SEND IN -ML

DRAFT LABEL FOR ZONASTAT-D

RESTRICTED USE PESTICIDE

For retail sale to and use only by Certified Applicators or persons under their direct supervision of the following organizations and their designated wildlife management personnel and only for those uses covered by the Certified Applicator's certification:

- Department of Interior and all its designated agents
- National Park Service, US Fish & Wildlife Service, Bureau of Land Management
- USDA and all its designated agents (i.e., U.S. Forest Service, Animal and Plant Health Inspection Service)
- State wildlife agencies and applicators acting under licenses issued by state wildlife agencies. ~~State Agencies for agriculture/livestock & wildlife~~
- Federally recognized Indian Tribes
- Department of Defense
- Humane Society of the United States

Each Responsible Authority deer intended to be treated with Zonastat-D must sign a certification of use prior to the administration of the vaccine to any animals. The certification statement is attached to this label.

Sublabel B

ZONASTAT-D

Zonastat-D is a porcine zona pellucida immunocontraceptive vaccine indicated for use in limiting the populations of white tailed deer (Odocoileus virginianus) and other members of the family Cervidae.

Active Ingredients:

Porcine zona pellucida (ZP3)(0.1%)	0.071%
Porcine zona pellucida ~~pellucida~~ (ZP1, ZP2, ZP4)(0.1%)	0.029%
Other Ingredients:	99.900%
Total	100.000%

This product contains 100 µg of PZP per 0.04 oz (0.5 mL)

EPA Reg. No. 86833-x
EPA Est. No. 090192-MT-001

Net Contents: 0.5 mL

Humane Society of the United States
700 Professional Drive
Gaithersburg, MD 20879

Expiration date: xx-xx-xxxx

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
IF ON SKIN OR CLOTHING	Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice. Needle stick or cut: clean wound immediately with soapy water and disinfect the wound with alcohol or other bactericidal solution. Contact with Freund's Complete Adjuvant: wipe skin clean with an ethanol soaked towelettes and wash with soapy water
IF INHALED	Move person to fresh air. If person is not breathing, call 911 or ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for treatment advice.
IF IN EYES	Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.
Have the product container or label with you when calling a poison control center or doctor or going for treatment. Accidental injection may cause infertility in women.	

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Harmful if absorbed through skin. Harmful if inhaled. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Avoid breathing spray mist.

Personal Protective Equipment (PPE)

Mixers, loaders and applicators must wear:

- Long sleeved shirt and long pants
- Shoes
- Socks
- Chemical resistant gloves made out of: barrier laminate, butyl rubber ≥14 mils, nitrile rubber≥14 mils, neoprene rubber ≥14 mils, natural rubber ≥14 mils, polyethylene, polyvinyl chloride ≥14 mils, or viton ≥14 mils

Environmental Hazards

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. -Do not contaminate water when disposing of equipment rinse waters or rinsate.

DIRECTIONS FOR USE
Restricted Use Pesticide

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

Read this entire label and follow all use directions and precautions.

Restrictions

- Only for use on female deer
- All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery.
- Do not expose children, pets, or other non-target animals to this product.
- Do not apply this product to food or feed.
- ~~Do not apply this product to deer being used as food.~~
- This product is only for use on female deer, which are defined as free-roaming deer, privately or publicly owned, that are capable of doing environmental damage.

Commented [1]: We propose deleting this statement – similar products do not contain similar statements.

Product Information

When injected into a female deer, ZonaStat-D stimulates the production of anti-zona pellucida (ZP) antibodies. These antibodies bind to the native ZP glycoproteins surrounding the egg of the target female, alter their conformation, and block sperm attachment.

Equipment Needed:

For Mixing
glass syringes, 5.0 cc, graduated at 0.2 cc, with Luer-Loc
1-1.25"~~.5 inch~~ 18-~~20~~-g disposable sterile needle ~~(thought you needed smaller needle?)~~
Freund's Adjuvant
PZP Solution (PZP antigen dissolved in phosphate buffered saline solution)
Luer-Loc connector
Plastic syringe for hand-injection
1" to 1.25" disposable sterile needle to use for injecting; with 18 - 20g needle bore.

Commented [2]: This is the correct size.

For Remote Dart Delivery
2.0 inch 18 g disposable sterile needle
1.0 cc dart with 1.25 inch or 1.25 inch barbless needle

Application Rate:

For maximum efficacy, ZonaStat-D is administered as an initial priming dose followed by a booster dose at least two weeks later. Efficacy is maintained by annual booster doses.

Initial Priming Dose: Is 1.0 cc of the PZP Solution/modified Freund's Complete Adjuvant emulsion. If followed by a booster dose, the priming dose may be administered at any time of the year. The priming dose alone is expected to reduce pregnancy rates by 55-70% for one year if administered one to three months prior to the onset of mating season. ~~(please revise this if needed to work for deer)~~

Commented [3]: Revisions are not needed for deer.

Booster Dose: Is 0.5 cc of the PZP Solution emulsified in 0.5 cc modified Freund's Incomplete Adjuvant ~~Adjuvant (which adjuvant?).~~ Administration of a single booster treatment at least 2 weeks after the administration of the priming dose is expected to reduce pregnancy rates by 90-95% for one year. Efficacy in subsequent years is maintained by administering an annual booster dose. ~~(please revise this if needed to work for deer)~~

Commented [4]: This is the proper name for the adjuvant.

Procedures:

Mixing

1. Gloves must be worn at all times
2. Attach the Luer-Lok connector to one of the glass syringes
3. Attach the 1.5 inch needle on the second glass syringe
4. Draw out 0.5 cc of adjuvant
5. Using the same syringe, draw up the 0.5 cc of PZP in phosphate buffered saline solution
6. Holding the syringe containing the vaccine very care (to prevent the plunger from slipping out), take off the needle and attach the syringe to the second syringe using the Luer-Lok connector.
7. Push the PZP solution-adjuvant mixture back and forth through the two syringes 100 times. The resulting emulsion will become thick and look white. THIS PROCEDURE IS VERY IMPORTANT AND IS RELATED TO THE PRESENTATION OF THE ANTIGEN AND THE SUBSEQUENT EFFICACY OF THE PRODUCT.
8. Make sure that all of the emulsion is in one syringe.
9. Holding the syringe containing the emulsion very carefully, remove the other syringe, leaving the Luer-Lok on the syringe containing the emulsion.

Application:

For Remote Dart Delivery, attach the 18 g 2 inch needle to the glass syringe containing the emulsion. Insert the needle into the body of the dart through the dart needle, and inject the contents of the syringe into the dart. Apply a small amount of Vaseline to the dart tip.

After the antigen solution and adjuvant are emulsified in the field and loaded into the dart, remotely inject ZonaStat-~~H~~-D intramuscularly in the hip or gluteus or hamstring muscles using a syringe dart fired from a CO_2 or cartridge-powered projection system.

Use the Pneu-Dart 1.0 cc dart with a 1.~~25~~ inch or 1.25 inch barbless needle for delivery.

The darts can be delivered using any of the following ~~rifles~~projectors, depending on the logistical requirements of the particular targeted population:

- Dan-Inject CO_2 rifle with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)
- Dan-Inject Pistol Grip CO2 Gun with a 13 mm barrel (for use at ranges of 5 meters to 20 meters)
- Pneu-Dart model 193 or 196 rifle (for use at ranges of up to 50 meters)
- Pneu-Dart model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)
- Pneu-Dart X-Caliber Gauged CO2 Long Range Projector (for use at ranges up to 50 meters)
- ~~Dan-Inject CO_2 rifle (Wildlife Pharmaceuticals) with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)~~
- ~~Dan-Inject Pistol Grip Blow Gun with a 13 mm barrel (for use at ranges of 5 meters to 20 meters)~~
- ~~Pneu-Dart model 193 rifle (for use at ranges of up to 50 meters)~~
- ~~Pneu-Dart model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)~~

~~Make sure that these models are still being marketed~~

All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its contents.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal

Pesticide Storage: The frozen PZP antigen expires after two years. Keep vials of PZP antigen frozen until ready for use. When transporting for use in the field, keep PZP antigen stored in a cooler, with ice packs. Once defrosted the PZP antigen expires after 24 hours. If transportation takes longer than 8 hours, store PZP antigen on dry ice in the cooler. Keep adjuvant refrigerated at +2° C to +8° C, but not frozen, until ready to be mixed with the PZP antigen. Store loaded darts in a cool dry area.

Pesticide Disposal: For any unused product dispose of as medical waste according to Federal, State, and Local regulations.

Container Disposal: Non-refillable container. Do not reuse or refill container. Dispose of expired material, preloaded syringes, used syringes as medical waste according to applicable Federal, State, and Local regulations. All used darts and needles are to be placed in a Sharps container and disposed of as medical waste according to applicable Federal, State and Local regulations.

Lewis, Marianne

From: Lewis, Marianne
Sent: Friday, August 19, 2016 9:03 AM
To: 'kathleen.sanzo@morganlewis.com'
Subject: FW: label comments for epa reg no 86833-1
Attachments: 86833-1 label comments 3august16.doc

Hi Kathleen,

Just checking in regarding the label comments for the ZonaStat that I sent to you on 8/3/16 wondering if you or the registrant had any questions. Am forwarding the label comments to you again just in case. Please let me know when the registrant will be sending the revised label to me. Did you find out anything on the Storage Stability and Corrosion Characteristics studies that are outstanding?

Thanks,

Marianne

From: Lewis, Marianne
Sent: Wednesday, August 03, 2016 1:38 PM
To: 'kathleen.sanzo@morganlewis.com' <kathleen.sanzo@morganlewis.com>
Subject: FW: label comments for epa reg no 86833-1

Attached is the revamped label for 86833-1 consisting of a sublabel A for the feral horses & burros and sublabel B for the deer. I have highlighted a few places where the two labels did not make any sense/need corrections from you. Please revise the label to follow this format and resubmit for review. Let me know if you have any questions.

Thanks,

Marianne

Marianne Lewis
Biologist
IVB3/RD
703 308-8043

Lewis, Marianne

From: Lewis, Marianne
Sent: Friday, August 12, 2016 11:44 AM
To: 'kathleen.sanzo@morganlewis.com'
Subject: 86833-1

Kathleen,

I noticed that you haven't submitted the storage stability and corrosion characteristics studies for 86833-1 (which was a condition of registration) to the Agency for review. Please let me know by the end of the day when you will be submitting these studies to us.

Thanks,

Marianne

Marianne Lewis
Biologist
IBV3/RD
703 308-8043

Sent 8/13/14

Dear Ms. Sanzo:

In order to move forward with the label amendment for your product, EPA Reg. No. 86833-1, please revise your label as follows:

RESTRICTED USE PESTICIDE

For retail sale to and use only by Certified Applicators or persons under their direct supervision of the following organizations and their designated wildlife management personnel and only for those uses covered by the Certified Applicator's certification:

- Department of Interior and all its designated agents
- National Park Service, US Fish & Wildlife Service, Bureau of Land Management
- USDA and all its designated agents (i.e., U.S. Forest Service, Animal and Plant Health Inspection Service)
- State Agencies for agriculture/livestock & wildlife
- Federally recognized Indian Tribes
- Department of Defense
- Humane Society of the United States

Each Responsible Authority must sign a certification of use prior to the administration of the vaccine to any animals. The certification statement is attached to this label.

Sublabel A

ZONASTAT-H

Zonastat-H is a porcine zona pellucida immunocontraceptive vaccine indicated for use in limiting the populations of wild and feral horses (Equus caballus) and burros (Equus asinus).

Active Ingredients:

Porcine zona pellucida (ZP3)(0.1%)	0.071%
Porcine zona pelluciad (ZP1, ZP2, ZP4)(0.1%)	0.029%
Other Ingredients:	99.900%
Total	100.000%

This product contains 100 µg of PZP per 0.04 oz (0.5 mL)

EPA Reg. No. 86833-x
EPA Est. No. 090192-MT-001

Net Contents: 0.5 mL

Humane Society of the United States
700 Professional Drive
Gaithersburg, MD 20879

Expiration date: (since the frozen PZP antigen expires after 2 years – label needs to have an expiration date on it.)

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
IF ON SKIN OR CLOTHING	Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice. Needle stick or cut: clean wound immediately with soapy water and disinfect the wound with alcohol or other bactericidal solution. Contact with Freund's Complete Adjuvant: wipe skin clean with an ethanol soaked towelettes and wash with soapy water
IF INHALED	Move person to fresh air. If person is not breathing, call 911 or ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for treatment advice.
IF IN EYES	Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.
Have the product container or label with you when calling a poison control center or doctor or going for treatment. Accidental injection may cause infertility in women.	

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Harmful if absorbed through skin. Harmful if inhaled. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Avoid breathing spray mist.

Personal Protective Equipment (PPE)

Mixers, loaders and applicators must wear:

- Long sleeved shirt and long pants
- Shoes
- Socks
- Chemical resistant gloves made out of: barrier laminate, butyl rubber ≥14 mils, nitrile rubber≥14 mils, neoprene rubber ≥14 mils, natural rubber ≥14 mils, polyethylene, polyvinyl chloride ≥14 mils, or viton ≥14 mils

Environmental Hazards

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment rinse waters or rinsate.

DIRECTIONS FOR USE

Restricted Use Pesticide

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

Read this entire label and follow all use directions and precautions.

Restrictions

- Only for use on female wild and feral horses and burros
- All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery.
- Do not expose children, pets, or other non-target animals to this product.
- Do not apply this product to food or feed.
- Do not apply this product to horses or burros being used as food.
- This product is only for use on female wild and feral horses and burros, which are defined as free-roaming horses or burros, privately or publicly owned, that are capable of doing environmental damage.

Product Information

When injected into a female wild and feral horse or burro, ZonaStat-D stimulates the production of anti-zona pellucida (ZP) antibodies. These antibodies bind to the native ZP glycoproteins surrounding the egg of the target female, alter their conformation, and block sperm attachment preventing conception.

Equipment Needed:

<u>For Mixing</u>
glass syringes, 5.0 cc, graduated at 0.2 cc, with Luer-Loc
1.5 inch 18 g disposable sterile needle
Freund's Adjuvant
PZP Solution (PZP antigen dissolved in phosphate buffered saline solution)
Luer-Loc connector

<u>For Hand Delivery</u>

3 cc disposable plastic syringe w/Luer-Loc
1.5 inch 18 g disposable sterile needle

For Jab-Stick Delivery
Jab Stick
3 cc disposable plastic syringe with Luer-Loc
1.5 inch 14 g disposable sterile needle

For Remote Dart Delivery
2.0 inch 18 g disposable sterile needle
1.0 cc dart with 1.25 inch or 1.5 inch barbless needle

Application Rate:

For maximum efficacy, ZonaStat-H is administered as an initial priming dose followed by a booster dose at least two weeks later. Efficacy is maintained by annual booster doses.

Initial Priming Dose: Is 0.5 cc of the PZP Solution emulsified with 0.5 cc modified Freund's Complete Adjuvant. If followed by a booster dose, the priming dose may be administered at any time of the year. The priming dose alone is expected to reduce pregnancy rates by 55-70% for one year if administered one to three months prior to the onset of mating season.

Booster Dose: Is 0.5 cc of the PZP Solution emulsified in 0.5 cc modified Freund's Incomplete Adjuvant (which adjuvant?). Administration of a single booster treatment at least 2 weeks after the administration of the priming dose is expected to reduce pregnancy rates by 90-95% for one year. Efficacy in subsequent years is maintained by administering an annual booster dose.

Procedures:

Mixing

1. Gloves must be worn at all times
2. Attach the Luer-Lok connector to one of the glass syringes
3. Attach the 1.5 inch needle on the second glass syringe
4. Draw out 0.5 cc of adjuvant
5. Using the same syringe, draw up the 0.5 cc of PZP in phosphate buffered saline solution
6. Holding the syringe containing the vaccine very care (to prevent the plunger from slipping out), take off the needle and attach the syringe to the second syringe using the Luer-Lok connector.
7. Push the PZP solution-adjuvant mixture back and forth through the two syringes 100 times. The resulting emulsion will become thick and look white. THIS PROCEDURE IS VERY IMPORTANT AND IS RELATED TO THE

PRESENTATION OF THE ANTIGEN AND THE SUBSEQUENT EFFICACY OF THE PRODUCT.

8. Make sure that all of the emulsion is in one syringe.
9. Holding the syringe containing the emulsion very carefully, remove the other syringe, leaving the Luer-Lok on the syringe containing the emulsion.

Application:

For Hand Delivery Injection, attach a 2.0 or 3.0 cc plastic syringe to the glass syringe via the Luer-Lok, and inject the emulsion into the plastic syringe. After loading the plastic syringe, disconnect the glass syringe and connect an 18 g 1.5 inch needle to the plastic syringe containing the emulsion.

For Jab Stick Delivery, place the nose of the plastic syringe tightly into the Luer-Lok and inject the emulsion from the glass syringe into the plastic syringe. After filling the plastic syringe, remove the glass syringe and attach the 14 g 1.5 inch needle to the plastic syringe containing the emulsion. Place the plastic syringe into the jab stick.

For Remote Dart Delivery, attach the 18 g 2 inch needle to the glass syringe containing the emulsion. Insert the needle into the body of the dart through the dart needle, and inject the contents of the syringe into the dart. Apply a small amount of Vaseline to the dart tip.

After the antigen solution and adjuvant are emulsified in the field and loaded into the dart, remotely inject ZonaStat-H intramuscularly in the hip or gluteus or hamstring muscles using a syringe dart fired from a CO_2 or cartridge-powered projection system.

Use the Pneu-Dart 1.0 cc dart with a 1.25 inch or 1.5 inch barbless needle for delivery.

The darts can be delivered using any of the following rifles, depending on the logistical requirements of the particular targeted population:

- Dan-Inject CO_2 rifle (Wildlife Pharmaceuticals) with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)
- Dan-Inject Pistol Grip Blow Gun with a 13 mm barrel (for use at ranges of 5 meters to 20 meters)
- Pneu-Dart model 193 rifle (for use at ranges of up to 50 meters)
- Pneu-Dart model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)
  Make sure that these models are still being marketed

All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its contents.

STORAGE AND DISPOSAL
Do not contaminate water, food or feed by storage or disposal

Pesticide Storage: The frozen PZP antigen expires after two years. Keep vials of PZP antigen frozen until ready for use. When transporting for use in the field, keep PZP antigen stored in a cooler, with ice packs. Once defrosted the PZP antigen expires after 24 hours. If transportation takes longer than 8 hours, store PZP antigen on dry ice in the cooler. Keep adjuvant refrigerated at +2° C to +8° C, but not frozen, until ready to be mixed with the PZP antigen. Store loaded darts in a cool dry area.

Pesticide Disposal: For any unused product dispose of as medical waste according to Federal, State, and Local regulations.

Container Disposal: Non-refillable container. Do not reuse or refill container. Dispose of expired material, preloaded syringes, used syringes as medical waste according to applicable Federal, State, and Local regulations. All used darts and needles are to be placed in a Sharps container and disposed of as medical waste according to applicable Federal, State and Local regulations.

RESTRICTED USE PESTICIDE

For retail sale to and use only by Certified Applicators or persons under their direct supervision of the following organizations and their designated wildlife management personnel and only for those uses covered by the Certified Applicator's certification:

- Department of Interior and all its designated agents
- National Park Service, US Fish & Wildlife Service, Bureau of Land Management
- USDA and all its designated agents (i.e., U.S. Forest Service, Animal and Plant Health Inspection Service)
- State Agencies for agriculture/livestock & wildlife
- Federally recognized Indian Tribes
- Department of Defense
- Humane Society of the United States

Each Responsible Authority deer intended to be treated with Zonastat-D must sign a certification of use prior to the administration of the vaccine to any animals. The certification statement is attached to this label.

Sublabel B

ZONASTAT-D

Zonastat-D is a porcine zona pellucida immunocontraceptive vaccine indicated for use in limiting the populations of white tailed deer (Odocoileus virginianus) and other members of the family Cervidae.

Active Ingredients:

Porcine zona pellucida (ZP3)(0.1%)	0.071%
Porcine zona pelluciad (ZP1, ZP2, ZP4)(0.1%)	0.029%
Other Ingredients:	99.900%
Total	100.000%

This product contains 100 µg of PZP per 0.04 oz (0.5 mL)

EPA Reg. No. 86833-x
EPA Est. No. 090192-MT-001

Net Contents: 0.5 mL

Humane Society of the United States
700 Professional Drive
Gaithersburg, MD 20879

Expiration date: (since the frozen PZP antigen expires after 2 years – label needs to have an expiration date on it.)

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID	
IF ON SKIN OR CLOTHING	Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice. Needle stick or cut: clean wound immediately with soapy water and disinfect the wound with alcohol or other bactericidal solution. Contact with Freund's Complete Adjuvant: wipe skin clean with an ethanol soaked towelettes and wash with soapy water
IF INHALED	Move person to fresh air. If person is not breathing, call 911 or ambulance, then give artificial respiration, preferably mouth-to-mouth, if possible. Call a poison control center or doctor for treatment advice.
IF IN EYES	Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.
Have the product container or label with you when calling a poison control center or doctor or going for treatment. Accidental injection may cause infertility in women.	

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals

Harmful if absorbed through skin. Harmful if inhaled. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Avoid breathing spray mist.

Personal Protective Equipment (PPE)

Mixers, loaders and applicators must wear:

- Long sleeved shirt and long pants
- Shoes
- Socks
- Chemical resistant gloves made out of: barrier laminate, butyl rubber ≥14 mils, nitrile rubber≥14 mils, neoprene rubber ≥14 mils, natural rubber ≥14 mils, polyethylene, polyvinyl chloride ≥14 mils, or viton ≥14 mils

Environmental Hazards

Do not apply this product directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment rinse waters or rinsate.

DIRECTIONS FOR USE

Restricted Use Pesticide

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation.

Read this entire label and follow all use directions and precautions.

Restrictions

- Only for use on female deer
- All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery.
- Do not expose children, pets, or other non-target animals to this product.
- Do not apply this product to food or feed.
- Do not apply this product to deer being used as food.
- This product is only for use on female deer, which are defined as free-roaming deer, privately or publicly owned, that are capable of doing environmental damage.

Product Information

When injected into a female deer, ZonaStat-D stimulates the production of anti-zona pellucida (ZP) antibodies. These antibodies bind to the native ZP glycoproteins surrounding the egg of the target female, alter their conformation, and block sperm attachment.

Equipment Needed:

<u>For Mixing</u>
glass syringes, 5.0 cc, graduated at 0.2 cc, with Luer-Loc
1.5 inch 18 g disposable sterile needle (thought you needed smaller needle?)
Freund's Adjuvant
PZP Solution (PZP antigen dissolved in phosphate buffered saline solution)
Luer-Loc connector

<u>For Remote Dart Delivery</u>
2.0 inch 18 g disposable sterile needle
1.0 cc dart with 1.25 inch or 1.5 inch barbless needle

Application Rate:

For maximum efficacy, ZonaStat-D is administered as an initial priming dose followed by a booster dose at least two weeks later. Efficacy is maintained by annual booster doses.

Initial Priming Dose: Is 1.0 cc of the PZP Solution/modified Freund's Complete Adjuvant emulsion. If followed by a booster dose, the priming dose may be administered at any time of the year. The priming dose alone is expected to reduce pregnancy rates by 55-70% for one year if administered one to three months prior to the onset of mating season. (please revise this if needed to work for deer)

Booster Dose: Is 0.5 cc of the PZP Solution emulsified in 0.5 cc modified Freund's Incomplete Adjuvant (which adjuvant?). Administration of a single booster treatment at least 2 weeks after the administration of the priming dose is expected to reduce pregnancy rates by 90-95% for one year. Efficacy in subsequent years is maintained by administering an annual booster dose. (please revise this if needed to work for deer)

Procedures:

Mixing

1. Gloves must be worn at all times
2. Attach the Luer-Lok connector to one of the glass syringes
3. Attach the 1.5 inch needle on the second glass syringe
4. Draw out 0.5 cc of adjuvant
5. Using the same syringe, draw up the 0.5 cc of PZP in phosphate buffered saline solution
6. Holding the syringe containing the vaccine very care (to prevent the plunger from slipping out), take off the needle and attach the syringe to the second syringe using the Luer-Lok connector.
7. Push the PZP solution-adjuvant mixture back and forth through the two syringes 100 times. The resulting emulsion will become thick and look white. THIS PROCEDURE IS VERY IMPORTANT AND IS RELATED TO THE PRESENTATION OF THE ANTIGEN AND THE SUBSEQUENT EFFICACY OF THE PRODUCT.
8. Make sure that all of the emulsion is in one syringe.
9. Holding the syringe containing the emulsion very carefully, remove the other syringe, leaving the Luer-Lok on the syringe containing the emulsion.

Application:

For Remote Dart Delivery, attach the 18 g 2 inch needle to the glass syringe containing the emulsion. Insert the needle into the body of the dart through the dart needle, and inject the contents of the syringe into the dart. Apply a small amount of Vaseline to the dart tip.

After the antigen solution and adjuvant are emulsified in the field and loaded into the dart, remotely inject ZonaStat-H intramuscularly in the hip or gluteus or hamstring muscles using a syringe dart fired from a CO_2 or cartridge-powered projection system.

Use the Pneu-Dart 1.0 cc dart with a 1.25 inch or 1.5 inch barbless needle for delivery.

The darts can be delivered using any of the following rifles, depending on the logistical requirements of the particular targeted population:

- Dan-Inject CO_2 rifle (Wildlife Pharmaceuticals) with a 13 mm barrel (for use at ranges of 10 meters to 40 meters)
- Dan-Inject Pistol Grip Blow Gun with a 13 mm barrel (for use at ranges of 5 meters to 20 meters)
- Pneu-Dart model 193 rifle (for use at ranges of up to 50 meters)
- Pneu-Dart model 389 cartridge-fired rifle (for use at ranges of up to 50 meters)
  Make sure that these models are still being marketed

All darts are to be recovered after delivery. Use neon orange or green darts to facilitate recovery. Examine all fired darts after recovery to determine if the charge fired and the plunger fully expelled its contents.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal

Pesticide Storage: The frozen PZP antigen expires after two years. Keep vials of PZP antigen frozen until ready for use. When transporting for use in the field, keep PZP antigen stored in a cooler, with ice packs. Once defrosted the PZP antigen expires after 24 hours. If transportation takes longer than 8 hours, store PZP antigen on dry ice in the cooler. Keep adjuvant refrigerated at +2° C to +8° C, but not frozen, until ready to be mixed with the PZP antigen. Store loaded darts in a cool dry area.

Pesticide Disposal: For any unused product dispose of as medical waste according to Federal, State, and Local regulations.

Container Disposal: Non-refillable container. Do not reuse or refill container. Dispose of expired material, preloaded syringes, used syringes as medical waste according to applicable Federal, State, and Local regulations. All used darts and needles are to be placed in a Sharps container and disposed of as medical waste according to applicable Federal, State and Local regulations.

Please submit these label changes back to me via email (lewis.marianne@epa.gov) as soon as possible so that I can proceed with this action and stamp off on a clean label.

If you have any questions please call or email.

Thanks,

Marianne Lewis
Biologist
IRB/RD
703 308-8043

Fee for Service {979421&~

This package includes the following

- ○ New Registration
- ◉ Amendment

☐ Studies? ☐ Fee Waiver?

☐ volpay % Reduction: ___

for Division

- ○ AD
- ○ BPPD
- ◉ RD

Risk Mgr. 7

Receipt No. S-	979421
EPA File Symbol/Reg. No.	86833-1
Pin-Punch Date:	1/6/2016

☐ This item is NOT subject to FFS action.

Action Code:

Requested: ?

Granted: R390

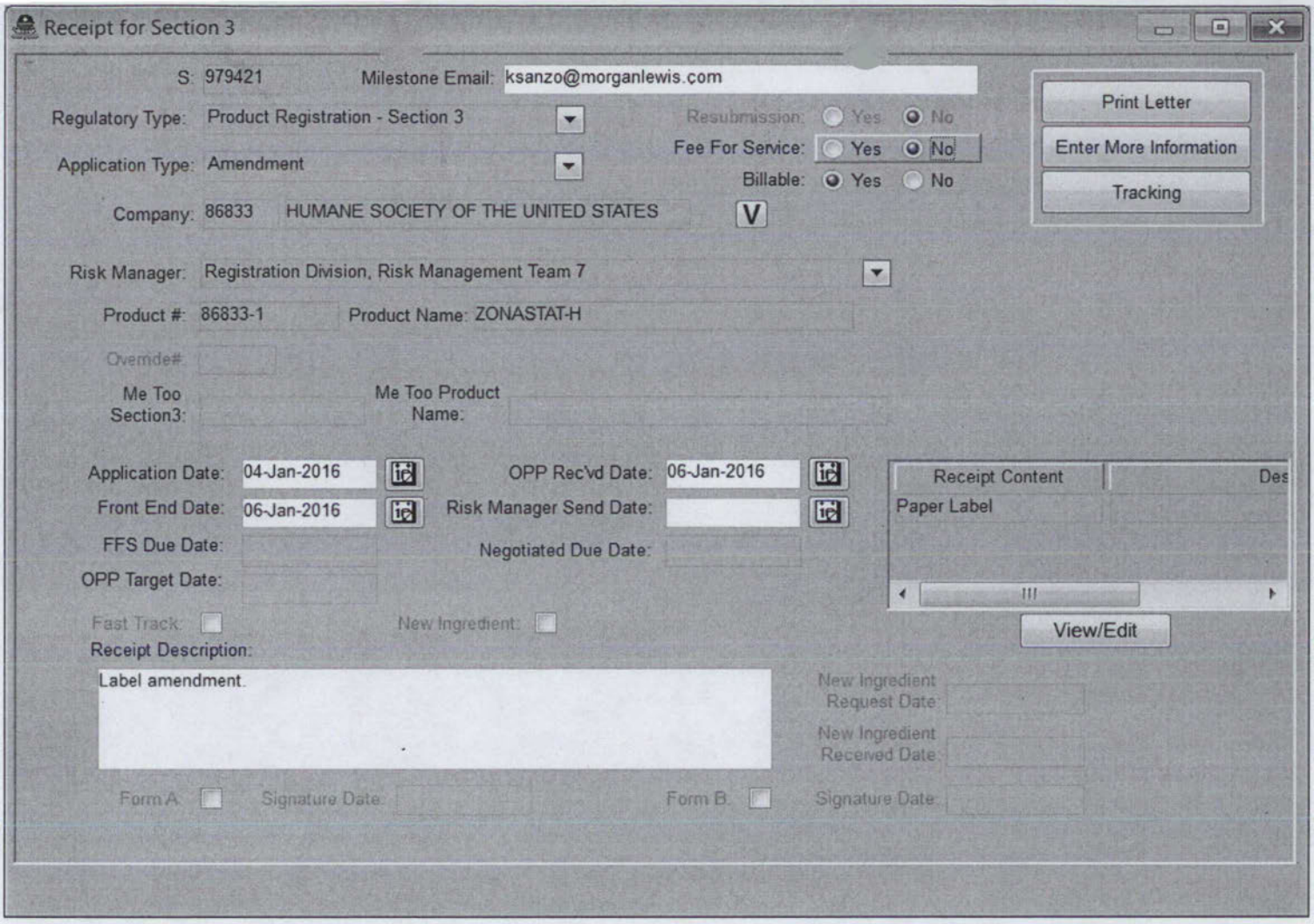
Amount Due: $ 3988.00

Parent/Child Decisions:

▣ Inert Cleared for Intended Use ▣ Uncleared Inert in Product

Reviewer: Kay Montague Date: 1/11/16

Remarks: Expanding use to deer - includes rationale/data for review.


Receipt for Section 3
S: 979421
Milestone Email: ksanzo@morganlewis.com
Regulatory Type: Product Registration - Section 3
Application Type: Amendment
Company: 86833 HUMANE SOCIETY OF THE UNITED STATES
Resubmission: Yes No
Fee For Service: Yes No
Billable: Yes No
Print Letter
Enter More Information
Tracking
Risk Manager: Registration Division, Risk Management Team 7
Product #: 86833-1
Product Name: ZONASTAT-H
Ovemde#:
Me Too Section3:
Me Too Product Name:
Application Date: 04-Jan-2016
Front End Date: 06-Jan-2016
FFS Due Date:
OPP Target Date:
OPP Rec'vd Date: 06-Jan-2016
Risk Manager Send Date:
Negotiated Due Date:
Receipt Content
Des
Paper Label
View/Edit
Fast Track:
New Ingredient:
Receipt Description:
Label amendment.
New Ingredient Request Date:
New Ingredient Received Date:
Form A:
Signature Date:
Form B:
Signature Date:

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060 Print Form

United States Environmental Protection Agency Washington, DC 20460

[ ] Registration [X] Amendment [ ] Other

OPP Identifier Number

Application for Pesticide - Section I

1. Company/Product Number

2. EPA Product Manager: Meredith Laws

3. Proposed Classification: [ ] None [X] Restricted

4. Company/Product (Name): Humane Society of the United States

PM#: 7

5. Name and Address of Applicant *(Include ZIP Code)*

The Humane Society of the United States
2100 L Street NW, Washington, DC 20037

[ ] *Check if this is a new address*

6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. 86833-1

Product Name ZonaStat-H

Section - II

[X] Amendment - Explain below.

[ ] Resubmission in response to Agency letter dated _____

[ ] Notification - Explain below.

[ ] Final printed labels in response to Agency letter dated _____

[ ] "Me Too" Application.

[ ] Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

HSUS proposes to amend the registration to add use of the product with deer.

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging: [ ] Yes* [X] No

* *Certification must be submitted*

Unit Packaging: [X] Yes [ ] No

If "Yes" Unit Packaging wgt. / No. per container

Water Soluble Packaging: [ ] Yes [X] No

If "Yes" Package wgt / No. per container

2. Type of Container: [ ] Metal [X] Plastic [ ] Glass [ ] Paper [ ] Other (Specify) _____

3. Location of Net Contents Information: [X] Label [X] Container

4. Size(s) Retail Container: 0.0202 (0.5ml)

5. Location of Label Directions: [ ] On Label [X] On Labeling accompanying product

6. Manner in Which Label is Affixed to Product: [X] Lithograph [ ] Paper glued [ ] Stenciled [ ] Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
Holly Hazard	Senior Vice President	(301) 721.6624

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

6. Date Application Received (Stamped)

2. Signature: Holly Hazard

3. Title: Senior VP, Programs & Innovations

4. Typed Name: Holly Hazard

5. Date: 12/24/2015

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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DATA MATRIX

Date 12/24/2015	EPA Reg No./File Symbol 86833-1	Page 1 of 1
Applicant's/Registrant's Name & Address Humane Society of the United States, 2100 L St NW, Washington DC 20037	Product ZonaStat-D	

Ingredient

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
Series 810	Product Performance Test Guidelines		Humane Society of the United States	PL	
Series 830	Product Properties Test Guidelines		Humane Society of the United States	PL	
Series 835	Fate, Transport, and Transportation Guidelines		Humane Society of the United States	PL	
Series 835	Loss of PZP-emulsion (ZonaStat-H) Darts in Sub-		Humane Society of the United States	PER	
	urban Deer Studies				
Series 850	Ecological Effects Test Guidelines		Humane Society of the United States	PL	
Series 870	Health Effects Test Guidelines		Humane Society of the United States	PL	
Series 875	Occupational and Residential Exposure Test Guidelines		Humane Society of the United States	PL	

Signature	Name and Title	Date
Holly Hazard	Holly Hazard, Senior Vice President, Programs & Innovations	12/24/2015

EPA Form 8570-35 (9-97) Electronic and Paper versions available. Submit only Paper version.

Agency Internal Use Copy

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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DATA MATRIX

Date 12/24/2015	EPA Reg No./File Symbol 86833-1	Page 1 of 1
Applicant's/Registrant's Name & Address Humane Society of the United States, 2100 L St NW, Washington DC 20037	Product ZonaStat-D	

Ingredient

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note
[redacted]			Humane Society of the United States	PL	
			Humane Society of the United States	PL	
			Humane Society of the United States	PL	
			Humane Society of the United States	PER	
			Humane Society of the United States	PL	
			Humane Society of the United States	PL	
			Humane Society of the United States	PL	

Signature	Name and Title	Date
Holly Hazard	Holly Hazard, Senior Vice President, Programs & Innovations	12/24/2015

EPA Form 8570-35 (9-97) Electronic and Paper versions available. Submit only Paper version.

Public File Copy

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January 4, 2016

VIA FEDEX

Dr. Meredith Laws
Chief, Insecticide-Rodenticide Branch
Registration Division (7505P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Dear Dr. Laws:

The Humane Society of the United States ("HSUS") requests amendment of its registration for ZonaStat-H to add use as a contraceptive for the control of populations of white-tailed (*Odocoileus virginianus*) deer and other members of the family Cervidae. The ingredients, preparation, and handling of the amended registration (to be titled, "ZonaStat-D") are identical to those of ZonaStat-H; however, conditions of use will differ.

The active ingredient of ZonaStat-D, porcine zona pellucida (PZP), has been extensively studied in captive and free-ranging deer by the HSUS, as well as by other investigators under INAD 8840 from the Center for Veterinary Medicine of the FDA.

Review of Investigational Use of PZP-adjuvant Emulsion Formulations in Deer

Initial studies of PZP vaccines with white-tailed deer were conducted using emulsions of PZP in Freund's Complete Adjuvant (FCA) for priming injections, and PZP in Freund's Incomplete Adjuvant (FIA) for boosters. Modified Freund's Complete Adjuvant (MFA) replaced FCA in primer injections in field trials beginning in 2002, as described below. Except for the use of FCA instead of MFA in early field trials, PZP dosages, manufacturing methods, field

emulsification, and delivery methods are identical to those described in the existing registration for ZonaStat-H.

Efficacy of PZP in Deer

In the initial captive study, Turner et al. (1992) showed that an initial injection of PZP emulsified in FCA followed by one or two booster shots 3 and 6 weeks later of PZP emulsified in Freund's Incomplete Adjuvant (FIA) prevented pregnancy in all 7 treated female white-tailed deer, whereas 6 of 7 control does became pregnant. All shots were delivered remotely via blowgun. In follow-up experiments (Turner et al. 1996), a single autumn booster shot of PZP/FIA extended infertility an additional year, but fertility was restored to control levels within two years of treatment. Similar efficacy and reversibility results were obtained in semi-captive and free-roaming deer receiving 2-shot FCA/FIA preparations in other studies (McShea et al. 1997; Walter et al. 2002).

Efficacy of the PZP/FCA/FIA preparation appeared to be lower under field conditions at Fire Island National Seashore (FIIS) (Kirkpatrick et al. 1997; Naugle et al. 2002). From 1993-1997, 74-164 individually known (but untagged) does were treated via blowgun in late summer or early autumn with two-shot PZP/FCA-PZP/FIA preparations followed by annual boosters of PZP/FIA. Overall, 17.6% of treated does produced fawns, with frequency of pregnancy declining significantly with successive years of treatment (Naugle et al. 2002). Efficacy also improved as delivery techniques improved.

A long-term study of PZP in white-tailed deer has been conducted at the National Institute of Standards and Technology (NIST), Gaithersburg, MD, since 1996. Between 1996 and 2002, 21.4% of 295 FCA/FIA treatments resulted in the production of fawns. Here there was no trend with respect to number of years of treatment (chi-square = 1.29, df = 4, P = 0.864) (Thiele 1999; Rutberg 2005). At NIST, annual boosters were stopped in 1999 for 21 FCA/FIA deer and reversibility followed for up to 4 years. 42.9% of the does fawned in the spring immediately after boosters ceased, while the others remained infertile for up to 4 years.

Safety of PZP/FCA/FIA treatments also was excellent. Only 2 of 353 deer receiving PZP/FCA or PZP/FIA darts delivered by blowpipe at FIIS developed draining abscesses, both of which healed within two weeks (Naugle et al. 2002). None of 9 deer hand- or dart-injected with PZP/FCA and PZP/FIA at Groton-Long Point were observed with injection site reactions (Walter et al. 2002). PZP/FCA/FIA-treated female deer showed comparable or improved body condition relative to untreated deer in two studies (McShea et al. 1997; Walter et al. 2003).

Shideler et al. (2002) demonstrated that PZP/FCA/FIA treatments were also effective under field conditions in tule elk (*Cervus elaphus nannodes)*. Pregnancy rates over a three year period ranged from 4-6% among PZP-treated elk, vs. 32-77% among untreated elk.

Efficacy of Proposed ZonaStat-D Formulation in Deer. Beginning in 2002, FCA was replaced by MFA in field trials at NIST. Between 2002 and 2012, 80 female white-tailed deer (including adults, yearlings, and fawns) individually marked with unique numbered ear-tags received an initial injection of 100 µg PZP in MFA by hand or dart followed by a booster of 100 µg PZP in FIA delivered by dart. Fawning rates among females initially treated as yearlings or adults only (N=44) closely resembled those reported for FCA/FIA in Naugle et al. 2002, with 15.6% of treated females fawning in the year after initial treatment, and 10% or fewer fawning in most subsequent years (HSUS unpubl.; Table 1).

The efficacy of MFA as an adjuvant is also supported by results from its use in association with investigational timed-release pellet preparations (Rutberg et al. 2013).

Extensive zoo data support the effectiveness of the ZonaStat-D formulation or a modified version (using multiple treatments of PZP/FIA emulsions only) in exotic deer including fallow deer (*Dama dama*), axis deer (*Cervus axis*), and sika deer (*C. nippon*) (Frank et al. 2005). Fallow deer have been especially well-studied; Deigert et al. (2003) report 3 of 59 semi-captive (island) adult female fallow deer hand-injected with PZP/FMA and/or PZP/FIA emulsions produced fawns after one year of treatment, and 0 of 59 produced fawns after a second year of treatment.

Safety of ZonaStat-D Formulation in Deer. Injection site reactions are extremely rare in ZonaStat-D treated deer. At NIST, between 2004 and 2012 approximately 5 sterile granulomas have been observed in an estimated 454 dartings (~1.1%) (HSUS, unpubl.). No injection site reactions (or other health problems) were reported following multiple hand-injected administrations of PZP/MFA and/or PZP/FIA emulsions in 59 adult female fallow deer (Deigert et al. 2003).

Although analysis of survival data at NIST is still incomplete, we can report that of 52 female deer that were captured and tagged as fawns in 2002-2005 and survived until receiving their first ZonaStat-D formulation 1-3 years after capture, 38 (73%) were still alive in 2013 (HSUS, unpubl.). This suggests an annual survival rate of greater than 90% among treated females more than 2 years old. This is higher than the 81% annual adult female survival rate observed by Etter et al. (2002) in suburban Chicago and the overall estimated deer population survival rate of 78% (including treated and untreated adult females, yearlings, and males) observed at NIST between 1996 and 2004 (Rutberg and Naugle 2008a). At both field sites, deer-vehicle collisions

accounted for the majority of deer deaths; PZP-treated females at NIST were at no greater risk of dying due to deer-vehicle collisions than untreated females (Rutberg and Naugle 2008b). At the very least, the high survival rate for ZonaStat-D-treated females indicates that the treatments cause no long term adverse effects.

Conditions of use. Field preparation and mixing of the PZP/MFA/FIA emulsion preparation as experimentally tested at NIST under INAD 8840 is identical to that of ZonaStat-H as described in the current EPA registration.

The initial preparation (PZP/MFA emulsion) may be delivered to adult, yearling, or fawn female deer by hand at time of capture, or to adult and yearling deer by dart, using techniques as described in the ZonaStat-H registration (except that the dart is fitted with a .75" or 1" needle, as suitable for a smaller animal, rather than a 1.5" needle). Storage and packaging of the PZP emulsion for deer will be identical to those procedures currently approved for ZonaStat-H and described in the training manual previously reviewed by EPA.

EPA has expressed concern about greater risk of public exposure to and injury from lost darts when ZonaStat-D is used on deer in suburban settings. Frequency of PZP dart loss has varied from site to site, ranging from 0.9% at Fire Island National Seashore, New York, and 1.5% at Fripp Island, South Carolina (both urbanized sites), to 18.1% loss at the National Institute of Standards and Technology, Maryland (a research campus with extensive tracts of forest and open meadow and limited public access and use). Reasons for variability include distance the shot was taken, density of ground cover, and personnel experience, with distance of shot taken probably being the strongest explanatory factor: most shots are taken at 5-10 yards at Fire Island and Fripp, whereas most shots at NIST are taken from >20 yards (see Appendix I).

Intensive efforts to recover darts are prescribed in the attached training manual for ZonaStat-D (Appendix II) and will be stressed during training procedures. The training manual also cautions prospective applicators concerning the lower recovery rates for darts fired at greater than 20 yards.

Despite the suburban settings and the firing of nearly 4,000 darts at the three field sites above, only 10-12 lost darts have been recovered and returned by non-project personnel, and no injuries associated with lost darts have been reported to The HSUS or by any of its institutional collaborators. As noted in the original ZonaStat-H registration application (vol. IV, p. 7, and elsewhere), because discharge can only be triggered by a high speed impact against a nearly perpendicular surface, the darts used cannot discharge spontaneously or upon casual contact. As also noted in the original ZonaStat-H registration application (vol. VII, pp. 8), the antigen itself biodegrades under field conditions, and the emulsion on which the immunological effects depend

breaks down with 48 hours. Thus, even for lost darts, the probability of direct public exposure to an immunologically active emulsion is nil.

Other Agency Review of ZonaStat-D Applications for Deer. Use of PZP on free-roaming deer will also be subject to conditions imposed by state pesticide control boards. In addition, all applications of ZonaStat-D to free-roaming deer will require state wildlife agency review and approval under the permitting processes established by law and regulation in each state. In the past, permit applications for investigational deer contraception projects have required the submission for state agency review of protocols describing in detail the contraceptive agent, study site, animal handling and veterinary protocols, and other conditions of use. Applications of PZP to deer on federal land will also be subject to review under the National Environmental Policy Act (NEPA).

Please let us know if any additional information is required. We have attached the relevant EPA forms for amendment of the registration.

Sincerely,

Kathleen M. Sanzo

Kathleen M. Sanzo
Counsel for HSUS

Enclosures

REFERENCES

Deigert, F.A.; Duncan, A.E., Frank, K.M., Lyda, R.O., and Kirkpatrick, J.F. (2003). Immunocontraception of captive exotic species. III. Contraception and population management of fallow deer (*Cervus dama*). *Zoo Biology* **22**, 261-268.

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Walter, W. D., Pekins, P.J., Rutberg, A.T., and Kilpatrick, H.J. (2002). Evaluation of immunocontraceptive adjuvants, titers, and fecal pregnancy indicators in free-ranging white-tailed deer. *Wildlife Society Bulletin* **30**, 908-914.

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Table 1

Fawning rates among female white-tailed deer at the National Institute of Standards and Technology, MD, initially treated as yearlings or adults with PZP/MFA followed by consecutive annual PZP/FIA boosters (HSUS, unpubl.). (available upon request?)

Year	**Number Pregnant/Total (%)**
Year 0 (pre-treatment)	16/20 (80%)
Year 1 (post-treatment)	7/44 (15.9%)
Year 2	2/36 (5.6%)
Year 3	2/27 (7.4%)
Year 4	2/18 (11.1%)
Year 5	0/14 (0%)
Year 6	0/12 (0%)

Appendix

Loss of PZP-emulsion (ZonaStat-H) Darts in Three Suburban Deer Studies
Dr. Allen T. Rutberg and Rick Naugle

Summary. Risk factors for dart loss include longer-range shots, inexperience of darters, and complex physical environments. Rates of dart loss at our two urbanized sites, Fire Island National Seashore, NY, and Fripp Island, SC, have been extremely low (0.9% of darts fired at Fire Island and 1.5% at Fripp Island), totaling 34 darts lost during 22 years in the field (1.5 darts/year). The rate of dart loss was much higher at the National Institute of Standards and Technology (NIST), MD (18.1%), which supports large tracts of forest and open meadow and which was also used heavily for training inexperienced darters. At NIST, shots fired at less than 20 yards showed about half the loss rates (10.1%) of shots fired at greater than 20 yards (18.8%). Despite wide community awareness of the darting programs, very few lost darts have been found and returned to the research team by members of the public.

As with wild horses and burros, ZonaStat-H can be delivered to deer by hand injection or by dart fired from a blowpipe, short-range CO_2 pistol, or CO_2- or cartridge powered rifle. For remote delivery, shots may be taken at ranges of 5-50 yards, although shots exceeding 35 yards are rarely taken. The darts themselves are approximately 3" long (including needle), consisting of a tail piece, a 1 cc body containing the emulsion and the plunger that injects the emulsion, and a ¾" – 1" 14 gauge stainless steel needle with an open port at the tip. Both the tailpiece and the plunger are colored day-glo orange or green specifically to facilitate recovery **(Fig.1**); in earlier dart models, the dart body was also conspicuously colored. Because of the firing mechanism, the dart must be fired at an object and strike it at a near-perpendicular angle in order to discharge; it cannot discharge on casual contact.

Dart Recovery Rates at Fire Island National Seashore, New York, 1993-2009. Fire Island National Seashore is a sandy barrier island supporting a mosaic of residential neighborhoods and undeveloped areas (**Fig. 2).** Residential areas consist of beach houses at moderately high density, connected by a network of boardwalks. Undeveloped areas include low scrub and isolated marshy pockets.

Between 1993 and 2009, only 32 of 3372 darts fired (0.9%) were not recovered by field personnel **(Table 1)**. Of the 32, only one was later reported found and returned by a resident.

Because deer on Fire Island are highly habituated to people, the overwhelming majority of dartings took place at close range (5-15 yards), generally in backyards or along boardwalks. Experience level of darters varied, with the most inexperienced darters working between 1998-2005; although the frequency of lost darts was consistently low, the highest frequency of losses did occur at that time.

Dart Recovery Rates at the National Institute of Standards and Technology, Maryland 1999-2013. The National Institute of Standards and Technology (NIST) is a 1 mi^2 research campus in Gaithersburg, Maryland **(Fig. 3)**. The campus consists of research buildings, parking lots, some open grassy fields that are mown twice annually, other fields that are no longer mown, and woodlots in which brushy undergrowth is largely absent but which are carpeted with invasive grasses and woody debris.

Although darting with PZP commenced at NIST in 1996, recording of numbers of darts lost and the range at which shots were taken began in 1999. From 1999-2013, 324 of 1791 PZP darts fired at deer on the NIST campus (18.1%) were lost **(Table 2)**. More than 93% of all darts lost were fired from >20 yards. Calculating from the number of shots fired at known distances, 18.8% of shots fired at >20 yards were lost, whereas 10.1% of shots taken at <20 yards were lost. Thus the probability of being lost was 1.86 times higher for shots taken at >20 yards than for shots fired at <20 yards.

We note that the majority of the darts lost prior to 2006 were most likely associated with darting by less experienced personnel. Since 2006 most deer at the NIST site have become wary and difficult to dart, most shots are long (>35 yards), and most shots are taken at deer in high grass, trees, or other dense cover. However, it is likely that the most important single factor explaining the relatively high frequency of lost darts at NIST is the longer range at which shots have been taken.

Despite full awareness of the project by campus police and facilities maintenance personnel, and considerable public attention to the project, fewer than a dozen lost darts have been recovered and returned to project personnel. All darts recovered were found in woodlots during the winter.

Dart Recovery Rates at Fripp Island, South Carolina, 2006-2010. Fripp Island is a residential and resort community on a 3.5 mi^2 barrier island off the coast of South Carolina **(Fig. 4)**. Approximately 25% is residentially developed, with another 20-25% occupied by two golf courses; the remainder is salt marsh and small patches of dense oak-palm-pine maritime forest.

Between 2006 and 2010, 136 darts were fired at Fripp Island, and only 2 (1.5%) were lost (**Table 3**). Neither was found and returned.

Although Fripp includes much difficult ground, nearly all darting is conducted along roadsides and in front and back yards of private residences, where ground cover is lawn or lawn-like. In addition, deer mostly maintained their habituated state, and most darts were fired from within 15 yards of the target animal. Thus conditions at Fripp are more similar to Fire Island than to NIST.

Table 1. Dart losses at Fire Island National Seashore, 1993-2003

Year	# Darts Shot	# Lost	% Lost
1993	148	0	0.0%
1994	239	0	0.0%
1995	226	1	0.4%
1996	184	1	0.5%
1997	153	0	0.0%
1998	276	4	1.4%
1999	328	3	0.9%
2000	252	3	1.2%
2001	208	4	1.9%
2002	225	7	3.1%
2003	192	2	1.0%
2004	157	2	1.3%
2005	161	3	1.9%
2006	139	0	0.0%
2007	141	0	0.0%
2008	225	1	0.4%
2009	118	1	0.8%
Total	**3372**	**32**	**0.9%**

Table 2. Dart losses at the National Institute of Standards and Technology, Maryland, 1999-2013

Year	# Darts Shot	# Lost	% Lost	# Shot <20 yards	# Lost <20 yards	% Darts shot <20 yards lost	#Shot >20 yards	# Lost >20 yards	% Darts shot >20 yards lost
1999	124	13	10.5						
2000	169	57	33.7	25	6	24.0	128	43	33.6%
2001	128	4	3.1	26	0	0.0	99	4	4.0%
2002	149	26	17.4	20	2	10.0	125	23	18.4%
2003	147	20	13.6	11	1	9.1	132	18	13.6%
2004	183	29	15.8	15	1	6.7	158	22	13.9%
2005	186	32	17.2	18	0	0.0	160	27	16.9%
2006	139	13	9.4	27	3	11.1	108	8	7.4%
2007	74	10	13.5	12	1	8.3	62	9	14.5%
2008	105	15	14.3	14	2	14.3	91	13	14.3%
2009	114	29	25.4	9	2	22.2	104	26	25.0%
2010	83	18	21.7	2	0	0.0	81	18	22.2%
2011	65	13	20	3	0	0.0	61	13	21.3%
2012	69	27	39.1	0	0		69	27	39.1%
2013	56	18	32.1	6	1	16.7	50	17	34.0%
Total	**1791**	**324**	**18.1%**	**188**	**19**	**10.1%**	**1428**	**268**	**18.8%**

Table 3. Dart losses at Fripp Island, South Carolina, 2006-2010

Year	# Darts Shot	# Lost	% Lost
2006	12	0	0.0%
2007	33	0	0.0%
2008	28	0	0.0%
2009	27	1	3.7%
2010	36	1	2.8%
Total	**136**	**2**	**1.5%**

Fig. 1. 1 cc Pneu-dart®. (This model has a gel collar which darts used to administer ZonaStat-H lack.)

Fig. 2. Typical appearance of terrain on Fire Island National Seashore (FIIS), New York

Fig. 3. Typical appearance of terrain at the National Institute of Standards and Technology (NIST), Maryland

Fig. 4. Typical appearance of terrain at Fripp Island, South Carolina

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Petition Pursuant to Section 6(b) of the Federal Insecticide, Fungicide, and Rodenticide Act Requesting that the Administrator Conduct a Special Review to Consider Scientific Evidence Demonstrating the Need to Cancel the Registration of the Contraceptive *ZONASTAT-H* for Population Control of America's Wild Horses and Burros

AR-15-0000-9279

Photograph: Friends of Animals

Petition Submitted to the Administer of the United States Environmental Protection Agency

May 19, 2015

Petitioner

~~OPPRESSORS~~
FRIENDS
of ANIMALS

Friends of Animals
Western Region Office
7500 E. Arapahoe Rd., Suite 385
Centennial, CO 80112
720-949-7791

~~OPPRESSORS~~
FRIENDS
of ANIMALS

May 19, 2015

Via U.S. Certified Mail

Gina McCarthy, Administrator
U.S. Environmental Protection Agency
Office of the Administrator (1101A)
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Jack Housenger, Director
U.S. Environmental Protection Agency
Office of Pesticide Programs
Registration Division (7505P)
1200 Pennsylvania Ave., N.W.
Washington, D.C. 20460

Re: Registration No. 86833-1 (the Unconditional Registration of *Porcine Zona Pellucida* (PZP) under FIFRA Section 3(c)(5) as a Contraceptive to Control Populations of Wild Horses and Burros).

Dear Administrator McCarthy and Director Housenger,

Friends of Animals ("FoA") hereby petitions the U.S. Environmental Protection Agency ("EPA") requesting that the Administrator conduct a special review to consider scientific evidence demonstrating the need to cancel the registration of the contraceptive ZonaStat-H, the primary ingredient of which is *porcine zona pellucida* ("PZP"), for population control of wild horses *(Equus caballus)* and burros *(Equus asinus)* under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"). The registration for PZP (86833-1) was issued to the Humane Society of the United States on or about January 30, 2012.

Pursuant to Section 6(b) of FIFRA, 7 U.S.C. § 136d (b), if new information becomes available to the Administrator that a pesticide, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment, the Administrator may cancel its registration. Here, information is now available to the administrator regarding the unintended (and previously undisclosed) side effects on both the targeted mares and wild horses in general. This new information not only shows unreasonable adverse effects, but also indicates that use of PZP on wild horses likely violates the Free-Roaming Wild Horse and Burro Act ("WHBA"). PZP use is not

needed to comply with any of the population mandates under the WHBA. More importantly, PZP is causing undue physical, social and biological harm to America's wild horses, both individually and collectively; and its continued use may result in genetic bottleneck that can threaten the continued existence of these animals in the wild.

This petition, filed pursuant to 7 U.S.C. § 136(d)(b), 5 U.S.C. § 553(e) and 40 C.F.R. § 154.10, consists of this letter and the attached Statement of Reasons in support of the petitioned action, as well as all documents cited within which are hereby specifically incorporated by reference. FoA specifically requests the Administrator:

1. Conduct a Special Review, pursuant to 40 C.F.R. § 154.1 *et seq.*, to determine whether to initiate proceedings to cancel or reclassify Registration 86833-1;
2. Issue an order suspending Registration 86833-1 pursuant to 7 U.S.C. § 136d(c)(1) during the Special Review and/or proceedings to cancel or reclassify the registration; and
3. Hold a hearing pursuant to 7 U.S.C. § 136(d)(b)(2) to determine if Registration 86833-1 should be canceled or reclassified if it is determined that additional information is needed to act upon this Petition.

Please do not hesitate to contact me at (720) 949-7791 if you need more information. My address appears below and on the cover sheet of the petition.

Sincerely,

Michael Harris
Legal Director
Wildlife Law Program
Friends of Animals
Western Region Office
7500 E. Arapahoe Rd., Ste. 385
Centennial, CO 80112

STATEMENT OF REASONS
IN SUPPORT
OF PETITION PURSUANT TO SECTION 6(B) OF THE FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT REQUESTING THAT THE ADMINISTRATOR CONDUCT A SPECIAL REVIEW TO CONSIDER SCIENTIFIC EVIDENCE DEMONSTRATING THE NEED TO CANCEL THE REGISTRATION OF THE CONTRACEPTIVE *ZONASTAT-H* POPULATION CONTROL OF AMERICA'S WILD HORSES AND BURROS

MAY 19, 2015

Friends of Animals
Western Region Office
7500 E. Arapahoe Rd., Suite 385
Centennial, CO 80112
720-949-7791

A. Introduction.

Reduction of free-roaming horse and burro populations through use of contraception has been a goal of some researchers and animal welfare organizations since the early 1970s (Kirkpatrick, et al., 1990). Various methods have been attempted leading up to the use of PZP. Initially, fertility reduction was demonstrated by using an injectable microencapsulated testosterone propionate (mTP) in stallions which resulted in an 83% decrease in foaling by mares (Kirkpatrick, et al., 1990). Delivery of mTP was done by first immobilizing the stallions and then injecting them. This method of delivery incurred high costs and stress to the animal, resulting in a remote method of delivery. Though mTP was effective in stallions, remote delivery made it difficult to deliver enough steroid to make it effective (Kirkpatrick, et al., 1990).

Another option was tried which also utilized steroid-induced fertility control, but this time the mares were the target animal. The use of ethinylestradiol-progesterone Silastic® implants showed effectiveness, but once again much stress was placed on the target animal because the method of delivery required the mare to be captured, restrained, then undergo field surgery to place the implants peritoneally (Kirkpatrick, et al., 1990).

By 1990, the focus then turned to immunocontraception as an alternative to steroid-induced fertility control. Of primary focus was *porcine zona pellucida* ("PZP"), which is extracted from pig ovaries and is a composite of four different acidic glycoproteins, ZP1, ZP2, ZP3, and ZP4. The antibodies bind to the ZP glycoproteins that surround the egg of the injected animal, alter the glycoproteins' conformation, and block the attachment of sperm, thus preventing fertilization. The principle of efficacy of PZP in horses was first demonstrated by Liu et al. (1989) by inhibiting fertility for seven months in 12 of 14 captive fertile domestic and wild mares. The researchers inoculated the mares with four hand injections of PZP with aluminum hydroxide gel. As the aluminum hydroxide gel was found to be only moderately effective in most of the horses, it was therefore substituted by FCA and FIA (modified Freund's Complete Adjuvant, mFCA, or Freund's Incomplete Adjuvant, FIA) at 2-4 week intervals. A fifth booster injection was administered 6-9 months after the fourth injection. This study also demonstrated that anti-PZP antibody titers of 64% or greater were associated with effective contraception, and that a decline in contraceptive effect correlated with a decline in antibody titers.

On September 16, 2009, the Humane Society of the United States ("Humane Society") submitted an application to the U.S. Environmental Protection Agency ("EPA" or "Agency") for a first registration of ZonaStat-H. The active ingredient in ZonaStat-H is PZP. The requested application use was for the control of wild and feral horse and burro populations on private and public lands. The application proposed that ZonaStat-H be administered to target animals via intramuscular injection in hip or gluteus muscles· either by hand delivery (injection), jab-stick delivery, or remote (dart) delivery. ZonaStat-H consists of an emulsion of two components: (1) the antigen, a naturally occurring, chemically unmodified glycoprotein, PZP; and (2) an adjuvant.

The Agency published a Notice of Receipt for this first registration on January 27, 2010. It was disclosed in this notice that the Humane Society requested waivers for most of the studies ordinarily required from an applicant seeking a pesticide registration, including a toxicity study, ecological effects and environmental fate guideline study, and an efficacy study. The requested waivers were granted by EPA. The Humane Society was allowed to seek its registration based on several studies conducted in the 1990s regarding the efficacy of the drug as a wild horse and burro contraceptive. These studies conclude overall that PZP can be highly effective at reducing fertility rates among wild horses with little to no side effect. A majority of these reviews were published by Dr. Jay Kirkpatrick, a veterinarian that manufactures PZP for use on wild horses. The Humane Society and Dr. Kirkpatrick, however, did not consider the biological, social and behavioral effects the drug can have on wild horses.

Based upon the information provided by the Humane Society, EPA granted the registration on or about January 30, 2012. Since that time, PZP has been in widespread use to control wild horse populations. For example, the Bureau of Land Management, which has jurisdiction over the largest number of wild horse herds on federal public lands, has administered approximately 1944 doses of PZP to wild mares since 2012. *See* BLM, Wild Horse and Burro Fact Sheet (2015). The U.S. Forest Service has also used PZP on mares in the Carson National Forest and potentially elsewhere. Moreover, the use of contraception generally, and the use of PZP specifically, is advocated by the U.S. Geological Survey and the National Academy of Science. (USGS, 2015) (NAS, 2013). These endorsements are directly tied to EPA's grant of the registration to the Humane Society, a group that has long had its own vision of wild horse management based primarily on the use of a drug, PZP, it has championed. *See* HSUS, *Our Vision for Wild Horse Management in the U.S.* (2010).

Petitioners do not challenge EPA's conclusion that "[t]he articles submitted by the HSUS assigned MRID Number 4785980 I are acceptable in that they support the efficacy of ZonaStat-H as a contraceptive for the control of wild and feral horses and burros." However, research has now demonstrated changes in mare stress and reproductive physiology, in addition to changes in male behavior. For example, researchers now know that:

- Mares which change groups more often (such as those treated with PZP) can exhibit increased stress levels and that this increased stress is maintained for at least two weeks after the group changes occur (Nuñez, Adelman et al., 2014);
- Mares that receive PZP over extended periods are more likely to cycle, become pregnant, and subsequently give birth in the fall (Nuñez, Adelman et al., 2010) and winter (unpublished data) months. This is significant because offspring born at this time face nutritional and thermoregulatory challenges not experienced by their counterparts born during the normal foaling season (during the spring and summer), potentially making developmental benchmarks difficult to achieve (Sadleir, 1969);
- After contraception management, PZP recipients both attract and initiate more instances of reproductive behavior (Nuñez, Adelman et al., 2009) and are more

often the harem male's nearest neighbor during the fall and winter (Nuñez, 2011), indicating that group spreads are reduced. These changes can be important as horses typically spread out in the fall and winter months to find scare forage. Such changes represent an increase in energy expenditure and a potential decrease in nutrient intake during a time of year when sufficient energy reserves are at a premium (Sadleir, 1969);

- Mares treated for more consecutive years are more likely to exhibit the behavioral and physiological changes outlined above (Nuñez, Adelman et al., 2010), decreases in ovarian function, and perhaps, permanent infertility; and
- Where, as is often the case, the plan is to vaccinate non-reproductive females (those between 1 and 3 years old), it will preclude young mares from forming the important social attachments between males and females typically made when foals are conceived. Such changes could further affect herd dynamics (Nuñez, 2014).

This new information demonstrates that PZP generally causes unreasonable adverse effects on the environment which warrants the Agency's consideration as to whether to cancel or reclassify its registration of this pesticide as a method of controlling wild horse and burro populations. Specifically, PZP poses the risk of immediate physical damage to the dosed mares, can increase the mortality rate in foals born to treated mares after the PZP loses its effectiveness, can result in social disruptions among herds with treated mares that can damage long-term herd cohesion that is critical to the health of the animals, and places the wild horses at risk of a genetic bottleneck. None of these risks were considered as part of the pesticide's initial registration.

B. Legal Authority.

1. Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA").

The Administrator of the EPA may issue a notice of cancellation of a pesticide when the pesticide, when used in accordance with widespread and commonly recognized practice, causes unreasonable adverse effects on the environment. 7 U.S.C. § 136d(b) (2015). *Defenders of Wildlife v. Jackson*, 791 F. Supp. 2d 96, 102 (D.D.C. 2011); *Reckitt Benckiser, Inc. v. EPA*, 613 F.3d 1131, 1134 (D.D.C. 2010). This authority is discretionary, but if the Administrator refuses to commence the cancellation proceedings, the party requesting the cancellation has a right to demand a hearing in a Federal Court of Appeals outside the administrative agency. *Defenders of Wildlife*, 791 F. Supp. 2d at 102; *Reckitt Benckiser, Inc.*, 613 F.3d at 1134.

The phrase "unreasonable adverse effects on the environment" is defined within FIFRA as "any unreasonable risk to man or the environment, taking into account economic, social, and environmental costs and benefits of the use of any pesticide." 7 U.S.C. § 136(bb)(1) (2015). Cases applying this definition affirm the statutory language straightforwardly, quoting the definitional language within FIFRA. *Chem. Specialties Mfrs. Ass'n v. United States EPA*, 484 F. Supp. 513, 515-16 (D.D.C. 1980) (quoting 7 U.S.C. § 136(bb)(1)). The statute's language and its surrounding case law necessitate Administrative discretion because the statute specifically requires that the Administrator

balance the risks and benefits of continued registration of the pesticide. *Id.* at 516. Therefore, the EPA is empowered through FIFRA to make the ultimate determination, upon new evidence, that a substance registered as a pesticide poses such an unreasonable risk of adverse effect to the environment. *See Ciba-Geigy Corp. v. EPA*, 874 F.2d 277, 280 (5th Cir. 1989) (holding that FIFRA gives the EPA Administrator significant discretion to determine that possible bird kills are an unreasonable adverse effect despite the fact that they do not actually significantly reduce the bird population, and that cancellation proceedings are proper); *Envtl. Def. Fund v. EPA*, 510 F.2d 1292, 1297 (D.C. Cir. 1975) (holding that the EPA Administrator has broad discretion to make decisions regarding policy related to the public interest).

EPA, by regulation, has established a "Special Review" process to assist in determining whether to initiate procedures to cancel or reclassify the registration of a pesticide because that the pesticide may cause unreasonable adverse effects on the environment. 40 C.F.R. § 154.1. According to the regulations:

> The process is intended to ensure that the Agency assesses risks that may be posed by pesticides, and the benefits of use of those pesticides, **in an open and responsive manner**. The issuance of a Notice of Special Review means that the Agency has determined that one or more uses of a pesticide **may** pose significant risks and that, following the completion of the Special Review process, the Agency expects to initiate formal proceeding seeking to cancel, deny, reclassify, or require modifications to the registration of the product(s) in question unless it has been shown during the Special Review that the Agency's initial determination [in the Notice of Special Review] was erroneous, that the risks can be reduced to acceptable levels without the need for formal proceedings, or that the benefits of the pesticide's use outweigh the risks.

Id. (emphasis added).

The determination to issue a Notice of Special Review may be based, among other things, upon a validated test or other significant evidence that the use of the pesticide in question: (a) may result in residuals in the environment of nontarget organisms at levels which equal or exceed concentrations acutely or chronically toxic to such organisms; (b) may pose a risk to the continued existence of any endangered or threatened species under the Endangered Species Act; or (c) may otherwise pose a risk to the environment which is of sufficient merit to determine whether the use of the pesticide offers offsetting social, economic, and environmental benefits to justify its continued use. *See* 40 C.F.R. § 154.7.

The Administrator may consider whether to issue a Notice of Special Review on her own initiative or at the suggestion of any interested party.[1] 40 C.F.R. § 154.10. In making a

[1] Although the regulations are silent as to the form such a "suggestion" must or should take, the Administrative Procedure Act ("APA") provides that "[e]ach agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule." 5

determination on whether to issue a Notice of Special Review, the Administrator shall be guided by:

> The principle that the **burden of persuasion** that a pesticide product is entitled to registration or continued registration for any particular use or under any particular set of terms and conditions of registration **is always on the proponent(s) of registration**.

40 C.F.R. § 154.5 (emphasis added). Thus, in order to be entitled to a Special Review, a petitioner need only present *prima facie* evidence to the Administrator that the pesticide in question causes unreasonable adverse effects on the environment. Once the petitioner presents a facial case that cancelation or reclassification of a registration might be warranted, the burden to demonstrate otherwise shifts to the proponents of registration. *Envtl. Def. Fund v. EPA*, 548 F.2d 998, 1004 (D.C. Cir. 1976).

2. Wild Free-Roaming Horses and Burros Act ("WHBA").

Modern horses, zebras, and asses belong to the genus *Equus*, the only surviving genus in a once diverse family, *Equidae* (Kirkpatrick and Fazio, 2010). Based on fossil records, the genus *Equus* originated in North America about three to four million years ago and spread to Eurasia by crossing the Bering Land Bridge two to three million years ago. A great deal of paleontological data has led experts to estimate that the modern horse, *E. caballus*, originated about two million years ago in North America (Kirkpatrick and Fazio, 2010). The last North American extinction probably occurred between 11,000 and 13,000 years ago (Kirkpatrick and Fazio, 2010), although more recent extinctions for horses have been suggested (Haile, et al., 2009). The expansion of humans across the Bering Land Bridge has been suggested as a possible explanation for the extirpation of wild horses in North America 11,000 to 13,000 years ago (Harrington, 2002). Climate change and changes in North American vegetation also likely played a role (Hulbert, 1993; Sharp and Cerling, 1998). Had it not been for previous westward migration into northwest Russia and Asia, the horse would have faced complete extinction. Fortunately, horses did survive, and spread to nearly every continent (Kirkpatrick and Fazio, 2010).

In the mid-1500s, Spanish conquistadors brought horses with them to North America, and some escaped or were released from captivity onto western rangelands (Garrott and Oli, 2013). These horses eventually developed distinct behaviors from their domestic counterparts. The fact that horses were domesticated before they were reintroduced matters little from a biological or behavioral viewpoint, as the reintroduced species is identical to that which had formerly been eliminated (Kirkpatrick and Fazio, 2010).

U.S.C. § 553(e). Under the APA, the term "rule" means the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy . . . ." 5 U.S.C. § 551(4).

By 1900, there were two to seven million wild horses in the United States (Ryden, 1999; Thomas, 1979). However, the population began declining in the early 1900s due to human exploitation. In the 1920s, well over one hundred thousand horses were slaughtered and sold for chicken feed, pet food, and human consumption (McKnight, 1959). Furthermore, hunters and ranchers started killing wild horses and driving them off the land based on the belief that wild horses would damage the land or compete with commercial livestock grazing (Ryden, 1999).

It was not clear that there were too many horses, nor that the horses were actually damaging the land. Nonetheless, the United States Forest Service and the United States Grazing Service (the predecessor to the BLM) responded to pressure from ranchers by removing tens of thousands of wild horses from federal property and allowing people to poison water holes and slaughter them without limit (Cruise and Griffiths, 2010). As part of the plan to clear the range of wild horses, the government collaborated with rendering plants that paid hunters six cents per pound to remove horses (Cruise and Griffiths, 2010). According to one BLM official, "within a period of four years [1946 to 1950] [BLM] removed over 100,000 abandoned and unclaimed horses from Nevada ranges." (Cruise and Griffiths, 2010 p. 59). Officials estimated that fewer than 4,000 horses remained in Nevada by 1950 (Cruise and Griffiths, 2010 p. 60).

Many people, outraged at the practice of violently and systematically eliminating wild horses, encouraged Congress to pass the Hunting Wild Horses and Burros on Public Lands Act in 1959 (Ryden, 1999). The Act banned the hunting of wild horses on federal land from aircraft or motorized vehicles. 86 P.L. 234, 73 Stat. 470. After passage of this law, however, ranchers and others continued to sell and slaughter wild horses (Cruise and Griffiths, 2010).

In 1971 Congress passed the WHBA, 16 U.S.C. §§ 1331 *et seq.*, and found that, "wild free-roaming horses and burros are living symbols of the historic and pioneer spirit of the West; that they contribute to the diversity of life forms within the Nation and enrich the lives of the American people; and that these horses and burros are fast disappearing from the American scene." Upon finding this, Congress stated its policy was that "wild free-roaming horses and burros shall be protected from capture, branding, harassment, or death, and to accomplish this they are to be considered in the area where presently found as an integral part of the natural system of public lands." 16 U.S.C. § 1331.

WHBA requires BLM to "protect and manage wild free-roaming horses and burros as components of the public lands . . . in a manner that is designed to achieve and maintain a thriving, natural ecological balance on the public lands." 16 U.S.C. § 1333(a). Additionally, WHBA requires management of wild horses and burros to be at "the minimal feasible level." *Id.* To do so, for each herd management area ("HMA") , BLM must: (1) maintain a current inventory of wild horses in the management area, (2) "determine [the] appropriate management level" of wild horses that the HMA can sustain, and (3) determine the method of achieving the designated management level and managing horses within it. 16 U.S.C. § 1333(b)(1); 43 C.F.R. §§ 4710.2, 4710.3-1. An appropriate management level, according to BLM's Wild Horses and Burros Management Handbook, is "expressed as a population range

within which [wild horses] can be managed for the long term" in a given HMA without resulting in rangeland damage.

Lastly, WHBA requires BLM to make a determination that there are excess wild horses prior to gathering or removing any wild horses from the range. *See Colorado Wild Horse & Burro Coal., Inc. v. Salazar*, 639 F. Supp. 2d 87 (D.D.C. 2009). WHBA defines the term "excess" as animals that "must be removed from an area in order to preserve and maintain a thriving ecological balance and multiple-use relationship in that area." 16 U.S.C. § 1332(f). BLM's Wild Horses and Burros Management Handbook explains that: "Before issuing a decision to gather and remove animals, the authorized officer shall first determine whether excess [wild horses] are present and require immediate removal. In making this determination, the authorized officer shall analyze grazing utilization and distribution, trend in range ecological condition, actual use, climate (weather) data, current population inventory, wild horses and burros located outside the HMA in areas not designated for their long-term maintenance and other factors such as the results of land health assessments which demonstrate removal is needed to restore or maintain the range in a [thriving, natural ecological balance]."

C. *Prima Facie* Evidence That Warrants a Special Review Process.

Although the information regarding PZP used to support its registration in 2009—studies that almost all took place before 2010—is generally accurate regarding PZP efficacy, with regards to ecological and environmental effects it is outdated now. Recent research has demonstrated changes in mare stress and reproductive physiology, in addition to changes in male behavior. For example, we now know that mares which change groups more often (such as those treated with PZP) can exhibit increased stress levels and that this increased stress is maintained for at least two weeks after the group changes occur (Nuñez, Adelman et al., 2014). Short-lived stressful situations are commonplace for several species (Sapolsky, 2005); however, repeated increases in stress hormones can adversely affect cardiovascular and immune function and, in the most extreme cases, can result in adverse neurobiological effects (Sapolsky, 2005). In addition, recent research shows that PZP: (1) can cause irreversible physical damage to the treated mares; (2) can increase mortality of offspring post-PZP effectiveness; (3) can result in social disruption among herds with treated mares that can result in long-term herd disintegration; and (4) can create a genetic bottleneck that may ultimately extinguish the population as a whole.

1. PZP can cause irreversible physical damage to the treated mares.

Physical effects of PZP in the short term are ostensibly non-existent. But with repeated applications, researchers have continually discovered, the mares often experience ovulatory failure and permanent infertility. Even on Assateague Island, arguably the most publicized management success story, the mares treated over multiple birthing seasons often eventually experience ovulatory failure (Ransom, et al., 2013). In another study, researchers explored further and discovered that ovulation failure experienced by these horses correlates with only five to seven years of PZP treatment, directly contradicting the drug's apparent "reversibility" (Nuñez, et al., 2010). This timeframe for ovulatory failure corresponds to other studies' findings of decreased fertility in post-treated females. Even

after population managers have discontinued the PZP treatment in a given animal, the wild mares remain 38.5% less likely than their untreated counterparts to become pregnant in subsequent years (Ransom, et al., 2013). Other research has even shown that PZP's efficacy, upon initial treatment, is 97%, dropping to 87% between years one and five, and finally reaching 100% "after five or more consecutive applications," and even after the applications have ceased (Nuñez, et al., 2010). This is contrary to the assertion of its reversibility, as only five years of treatment is required to render the mare permanently infertile.

The ability of mares to become pregnant after treatment is dependent upon the number of consecutive treatments received. Mares treated for more consecutive years are more likely to exhibit the behavioral and physiological changes outlined above (Nuñez, Adelman et al., 2010), decreases in ovarian function (Kirkpatrick, Liu et al. 1990), and perhaps, permanent infertility. Shackelford mares for which treatment was halted in 2009 have yet to return to pre-contraception levels of fertility (Nuñez, 2014, unpublished data, see Figure 1). This effect is exacerbated in mares that received more consecutive treatments (Nuñez, 2014, unpublished data).

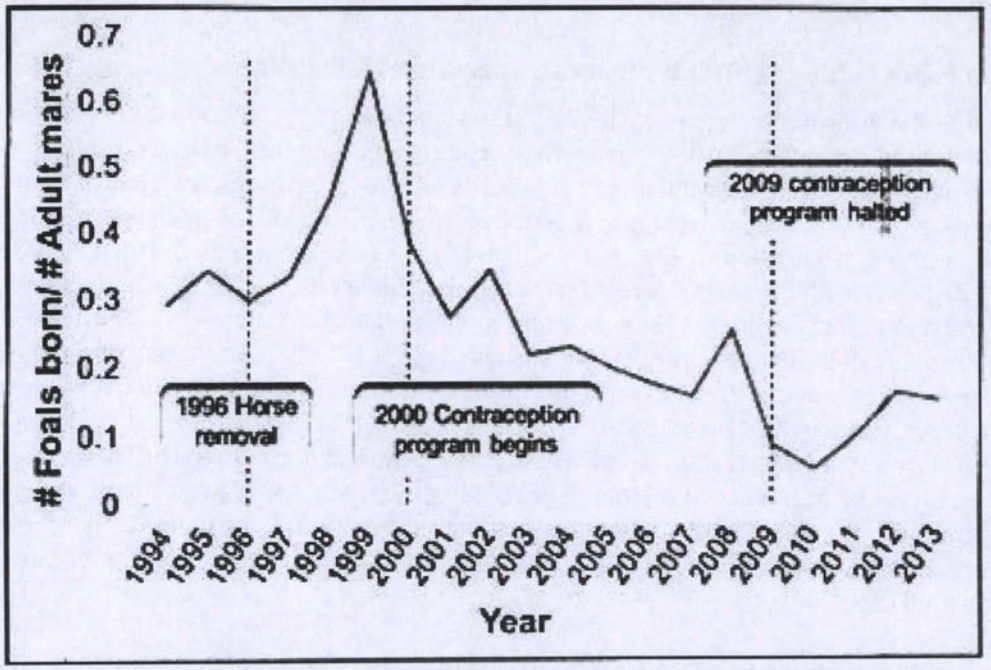

Figure 1. Pregnancy in Shackleford mares before, during and after contraception management.

2. PZP can increase mortality in foals post-PZP effectiveness.

When PZP is introduced into wild horse populations, it tends to have a cascading effect on the timing of conception and foaling in PZP treated mares (Liu, et al., 1989; Ransom, et al., 2014; Nuñez, et al., 2010; Madosky, et al., 2010). Jason Ransom's 2013 study found that large mammals, such as wild horses, breed according to seasonal cues like temperature and the amount of sunlight the animal is exposed to, or "photoperiod" (Ransom, et al., 2013). In the case of wild horses, these environmental factors result in

mostly springtime births, coinciding with peak forage availability (Ransom, et al., 2013). The abundance of forage is critical to meet the increased trophic needs of nursing mares and new foals (Ransom, et al., 2013). Births occurring at other times of the year, after forage availability has begun to decline, result in increased foal mortality. Ransom et al. found that the foals' chances of mortality increased 1.4% for every ten days after peak forage that birth occurred (2013). This may seem insignificant, but for foals born 180 days after the summer solstice (roughly around the winter solstice), the risk of mortality increases over 25%. Even if the foals survive their disadvantage, the reduction in forage availability can prevent them from reaching critical developmental milestones (Nuñez, et al., 2010). Mares birthing at times off the peak forage availability results in negative health outcomes for their foals, including developmental delays, as well as death. Mares treated with PZP are more likely to birth asynchronously with peak forage, making maternal treatment with PZP a major contributor to negative foal outcomes.

If the PZP vaccination is ineffective, or has lapsed, and the mare conceives, the foal has a greater likelihood of being born off of peak foraging times (Nuñez et al., 2010; Madosky et al 2010). The nearly yearlong gestation of the horses means that the breeding period occurs slightly before the summer solstice; foals conceived during this period are born approximately two to four weeks before the next summer solstice (Ransom, et al., 2013; Nuñez, et al., 2010). This is the ideal time for foals to be born because it corresponds with peak forage availability (Ransom, et al., 2013). The PZP, however, contributes to increased reproductive behaviors both from and towards the treated mares at suboptimal times of the year (Ransom, et al., 2010). For example, mares failing to conceive at or around the solstice will continue to exhibit reproductive behaviors well after forage has begun to decline. This increases the likelihood that a foal would be conceived, and therefore born, at a suboptimal time of the year (Ransom, et al., 2013). Without the trophic support of abundant forage, the likelihood of these foals' deaths is quantifiably increased as they are born later after the peak forage of the summer solstice (Ransom, et al., 2013).

It is true that other variables do affect the foals' survival, but all of the other variables are compounded by PZP treatment of females within the herd; none of them have the same detrimental effect as they do when they are compounded with PZP treatment (Ransom, et al., 2013). Furthermore, despite the existence of the other variables, the most significant variable to survival of foals born in later months is PZP treatment (Ransom, et al., 2013).

3. Herd cohesion is critical to the health of the horses, and interfering with the ability to bear foals damages that cohesion.

Wild horses organize themselves into herds or harems consisting of usually one lead stallion, one to several mares, and the herd's juvenile offspring (Nuñez et al 2009). The herd is generally socially stable, with each core adult remaining with the group for months or years (Nuñez, et al., 2009). In order for the herd to remain stable, however, each adult must remain within it; changes to the structure, which are typically rare, will disrupt the herd's stability, bringing with it elevated stress responses for many horses involved (Nuñez, et al., 2009). Stable herds also tend to correlate with increased foal survival (Madosky, et al., 2010). Overall, herd cohesion is vital to the health of the animals.

Multiple studies have shown that the most significant factor in maintaining herd cohesion is foal presence and pregnancy (Nuñez, et al., 2009; Madosky, et al., 2010). Mares who are pregnant or lactating tend to remain in their herds, while mares treated with PZP change herds and visit other herds more frequently (Madosky et al 2010). Changes to herd composition disrupts the normal social structure of the entire wild horse population necessarily; of course a mare's unsettled wandering affects not only the herd she abandons, but also the herd she joins (Madosky, et al., 2010). This disruption is felt throughout a wild horse population, especially when a majority of the mares within that population are treated with PZP (Madosky, et al., 2010; Ransom, et al., 2014; Nuñez, et al., 2009). It would not be just one mare traveling around to different herds, but could realistically be virtually all the mares, essentially destroying the social structure of the population and causing elevated stress levels to all the animals therein. Madosky's study indicates that PZP has a significant effect on mares' wandering, finding that the contracepted mares are 40% more likely to change herds than their non-contracepted counterparts (Madosky, et al., 2010). Another study specifically shows that herd fidelity negatively correlates with PZP application: as more horses are treated, the less faithful they are to the herd in which they normally live (Ransom, et al., 2014). In short, the herd disruption caused by PZP places wild horses at risk of reproductive failure (which as noted below can be another factor leading to a genetic bottleneck).

Stress to wild horses causes sustained elevated cortisol levels, which can be extremely physiologically damaging (Nuñez, et al., 2014). This stress can cause a multitude of adverse physical effects, including negative impacts to cardiovascular function, inhibition of reproduction, compromised immune response, and neurological issues (Nuñez, et al., 2014). Nuñez' study finds that mares transferring herds exhibit elevated cortisol levels for two weeks after their herd transfer, at levels not similarly exhibited in mares who remain with their herds (Nuñez, et al., 2014). For mares that change herds frequently, these stress levels can be elevated constantly. Elevated stress response to transferring herds also causes increased offspring mortality and increased parasite loads (Nuñez, et al., 2014). These effects impact the physical health of the horses, and because the effects are so widespread, these impacts can be felt throughout the wild horse populations.

4. Preventing some mares from producing foals can create a genetic bottleneck that may ultimately extinguish the population as a whole.

Prevention of reproduction can have significant genetic effects on the wild horse populations, in addition to the physical and social effects. First, by limiting the number of mares that are permitted to reproduce, managers limit future generations' genetic diversity. A similar problem occurred in the elephant seal population in the mid 1800s (Bonnell and Selander, 1974). Hunted to near extinction, an extremely small population in a small refugium of elephant seals remained, from which practically all extant elephant seals today descend (Bonnell and Selander, 1974). This dramatic reduction in population, followed by a population boom, created what is known as a "bottleneck" (Bonnell and Selander, 1974). While a genetic bottleneck does not necessarily eliminate a population, it often will exert pressure on the population that can reduce genetic fitness (Dunn and Byers, 2008). In a classic bottleneck situation inbreeding between individuals reduces the

long-term viability of the population (Heber and Briskie, 2010). Using immunocontraception on wild horse populations is not a classic bottleneck because the contracepted individuals remain within the population. But by controlling the fertility of a significant portion of the adult females, the same effect is achieved; only a few individuals are available to pass on their genes, ensuring that the next generation has significantly reduced genetic diversity than it would have had if immunocontraception had not been applied. If all of the members of a wild horse population are descended from the same few mares, eventually inbreeding will reduce the fitness of the population beyond the point of viability, potentially extinguishing the entire population.

Another genetic effect becomes apparent upon consideration of the fact that PZP works by stimulating the horse's own immune system into preventing fertilization of the egg (Ransom et al 2014). The drug is not 100% effective because not every mare's immune system is sufficiently responsive (Ransom, et al., 2014; Nuñez, et al., 2009). It is the mares with weaker immune systems that continue to pass on their genes; mares with the strongest immune systems are effectively contracepted (Ransom, et al., 2014). This may result in the prevention of strong immune systems from reproducing, and may destroy the ability of the wild horse in general to fight off infection in the future. This result could render the whole population sickly and frail and contribute to the population's possible extinction (Ransom, et al., 2014).

D. Regulatory Basis for Initiation of a Special Review.

1. PZP can result in residues in the environment of nontarget organisms—the foals of treated mares conceived and birthed post application—that equal or exceed concentrations that are toxic to those organisms.

In granting the Humane Society's waiver requests to fulfill the required ecological effects and environmental fate guideline studies, EPA determined that "[e]xposure to non-target organisms is not likely to occur because of the targeted nature of the application." Assuming that the targeted organism is the wild mare that is dosed with PZP, then given new information generated since Humane Society's 2009 application, this statement can no longer hold true. As discussed above, after the administered PZP is no longer effective to prevent conception, the drug's residual effect: (a) contributes to increased reproductive behaviors at suboptimal times; (b) increases the likelihood that birth will also occur at suboptimal times; and (c) and quantifiably increases the likelihood of the foal mortality. While it is true that PZP is not directly killing foals conceived post-PZP effectiveness (i.e., it is not poisoning the foal), residual PZP in the foal's pre-birth environment (its mother) is the reason for the increased mortality rate. Moreover, an increased mortality rate of up to 25% is significant. Petitioner has presented a *prima facia* case for initiating a Special Review based upon this consideration.

2. PZP may otherwise pose a previously undisclosed risk to the environment which is of sufficient magnitude to merit a Special Review.

Congress declared that "wild free-roaming horses and burros are living symbols of the historic and pioneer spirit of the West; that they contribute to the diversity of life forms within the Nation and enrich the lives of the American people; and that these horses and burros are fast disappearing from the American scene." Moreover, "they are to be considered in the area where presently found as an integral part of the natural system of public lands." In other words, wild horses are part of the western landscape and environment. Recent studies indicate that the use of PZP as a population control tool poses multiple risks to these animals that were never disclosed or considered during the FIFRA registration process. Whether it is physical damage to dosed mares, the increased mortality in foals born to previously treated mares, the disruption of herd cohesion that is critical to the health of the horses individually and as a herd, or the increased risk of a genetic bottleneck, PZP (even after just a couple of years of widespread use) poses a significant risk to these animals. Petitioner has presented a *prima facia* case for initiating a Special Review based upon this consideration.

3. The use of PZP violates the WHBA.

While the Agency's regulations only identify risk to species protected by the federal ESA as a specific criteria for initiation of a Special Review, wild horses and burros are protected by a species-specific act that seeks to protect them in ways similar to the ESA. Thus, Congress has declared that "wild free-roaming horses and burros shall be protected from capture, branding, **harassment, or death**, and to accomplish this they are to be considered in the area where presently found as an integral part of the natural system of public lands." Certainly, it is in the spirit of the regulations and FIFRA to consider whether a pesticide could violate a species-specific act when considering whether to initiate proceedings to cancel or reclassify the pesticide's registration. In this regard, new studies indicate that PZP use is harassing, and even killing, wild horses in ways not considered as part of the initial registration process. While it is true that the WHBA provides for an exception from these general mandates to protect wild horses in order to control their populations, this exception is both narrow (the animal must be deemed "excess") and can only be applied if the implementing agency (BLM or USFS) first completes certain statutory requirements. It may be that with regard to the decision to dose a particular mare the implementing agency can comply with the WHBA. However, the other horses in the herd that are not dosed with PZP (as well as the unborn foals) cannot be legally defined as "excessive" and, thus, the harassment or death to these animals caused by PZP violates the WHBA.

E. Conclusion.

Wild horses are not only a living embodiment of the spirit of the American West, but are also an important part of the ecosystem in which they live. The application of PZP to control wild horse fertility has long-term consequences that are already occurring, and will continue to occur, specifically reduction in the genetic fitness and viability of these majestic

and ecologically critical creatures. In order to preserve the wild horse population and the environment of the American West, the EPA Administrator should proceed with a Special Review to consider whether there are grounds to initiate proceedings to cancel or reclassify this insidious pesticide.

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*Indicates a book, which Petitioners have not enclosed with this petition. However, Petitioners can provide a copy of the relevant cited portions if requested.